

**Application  
for  
United States Letters Patent**

**To all whom it may concern:**

*Be it known that* we, Wai C. Wong, Bharat Lagu, Dhanapalan Nagarathnam,  
Mohammad R. Marzabadi and Charles Gluchowski

*have invented certain new and useful improvements in*

DIHYDROPYRIMIDINES AND USES THEREOF

*of which the following is a full, clear and exact description.*

Dihydropyrimidines and Uses Thereof

5 Throughout this application, various references are  
referred to within parentheses. Disclosures of these  
publications in their entireties are hereby  
incorporated by reference into this application to more  
fully describe the state of the art to which this  
10 invention pertains.

Background of the Invention

15 The designation " $\alpha_{1A}$ " is the appellation recently  
approved by the IUPHAR Nomenclature Committee for the  
previously designated " $\alpha_{1C}$ " cloned subtype as outlined  
in the 1995 Receptor and Ion Channel Nomenclature  
Supplement (Watson and Girdlestone, 1995). The  
20 designation  $\alpha_{1A}$  is used throughout this application and  
the supporting tables and figures to refer to this  
receptor subtype. At the same time, the receptor  
formerly designated  $\alpha_{1A}$  was renamed  $\alpha_{1D}$ . The new  
nomenclature is used throughout this application.  
Stable cell lines expressing these receptors are  
25 described herein; however, these cell lines were  
deposited with the American Type Culture Collection  
(ATCC) under the old nomenclature (infra).

30 Benign Prostatic Hyperplasia (BPH), also called Benign  
Prostatic Hypertrophy, is a progressive condition which  
is characterized by a nodular enlargement of prostatic  
tissue resulting in obstruction of the urethra. This  
results in increased frequency of urination, nocturia,  
a poor urine stream and hesitancy or delay in starting

the urine flow. Chronic consequences of BPH can include hypertrophy of bladder smooth muscle, a decompensated bladder and an increased incidence of urinary tract infection. The specific biochemical, histological and pharmacological properties of the prostate adenoma leading to the bladder outlet obstruction are not yet known. However, the development of BPH is considered to be an inescapable phenomenon for the aging male population. BPH is observed in approximately 70% of males over the age of 70. Currently, in the United States, the method of choice for treating BPH is surgery (Lepor, H., Urol. Clinics North Amer., 17, 651 (1990)). Over 400,000 prostatectomies are performed annually (data from 1986). A medicinal alternative to surgery is clearly very desirable. The limitations of surgery for treating BPH include the morbidity rate of an operative procedure in elderly men, persistence or recurrence of obstructive and irritative symptoms, as well as the significant cost of surgery.

$\alpha$ -Adrenergic receptors (McGrath, et. al. Med. Res. Rev., 9, 407-533, 1989) are specific neuroreceptor proteins located in the peripheral and central nervous systems on tissues and organs throughout the body. These receptors are important switches for controlling many physiological functions and, thus, represent important targets for drug development. In fact, many  $\alpha$ -adrenergic drugs have been developed over the past 40 years. Examples include clonidine, phenoxybenzamine and prazosin (treatment of hypertension), naphazoline (nasal decongestant), and apraclonidine (treating glaucoma).  $\alpha$ -Adrenergic drugs can be broken down into two distinct classes: agonists (clonidine and naphazoline are agonists), which mimic the receptor activation properties of the endogenous neurotransmitter norepinephrine, and antagonists (phenoxybenzamine and prazosin are antagonists), which act to block the effects of norepinephrine. Many of

these drugs are effective but also produce unwanted side effects (for example, clonidine produces dry mouth and sedation in addition to its antihypertensive effects).

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During the past 15 years a more precise understanding of  $\alpha$ -adrenergic receptors and their drugs has evolved through increased scientific scrutiny. Prior to 1977, only one  $\alpha$ -adrenergic receptor was known to exist. Between 1977 and 1988, it was accepted by the scientific community that at least two  $\alpha$ -adrenergic receptors-- $\alpha_1$  and  $\alpha_2$ --existed in the central and peripheral nervous systems. Since 1988, new techniques in molecular biology have led to the identification of at least six  $\alpha$ -adrenergic receptors which exist throughout the central and peripheral nervous systems:  $\alpha_{1A}$  (new nomenclature),  $\alpha_{1B}$ ,  $\alpha_{1D}$  (new nomenclature),  $\alpha_{2A}$ ,  $\alpha_{2B}$  and  $\alpha_{2C}$  (Bylund, D.B., FASEB J., 6, 832 (1992)). In many cases, it is not known precisely which physiological responses in the body are controlled by each of these receptors. In addition, current  $\alpha$ -adrenergic drugs are not selective for any particular  $\alpha$ -adrenergic receptor. Many of these drugs produce untoward side effects which may be attributed to their poor  $\alpha$ -adrenergic receptor selectivity.

Since the mid 1970's, nonselective  $\alpha$ -antagonists have been prescribed to treat BPH. In 1976, M. Caine, et al. (Brit. J. Urol., 48, 255 (1976)), reported that the nonselective  $\alpha$ -antagonist phenoxybenzamine was useful in relieving the symptoms of BPH. This drug may produce its effects by interacting with  $\alpha$ -receptors located on the prostate. However, this drug also produces significant side effects such as dizziness and asthenia which severely limit its use in treating patients on a chronic basis. More recently, the  $\alpha$ -adrenergic antagonists prazosin and terazosin have

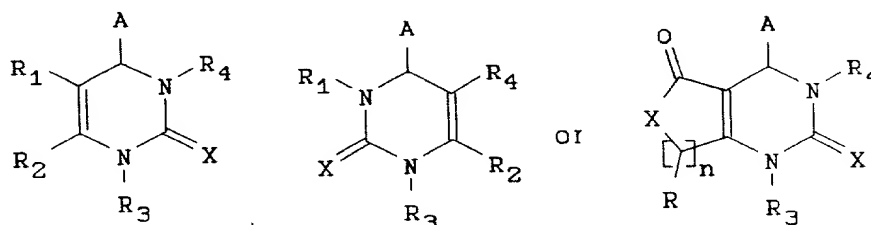


also been found to be useful for treating BPH. However, these drugs also produce untoward side effects. It has recently been discovered that the  $\alpha_{1A}$  receptor is responsible for mediating the contraction of human prostate smooth muscle (Gluchowski, C. et. al., WO 94/10989, 1994; Forray, C. et. al., Mol. Pharmacol. 45, 703, 1994). This discovery indicates that the  $\alpha_{1A}$  antagonists may be effective agents for the treatment of BPH with decreased side effects. Further studies have indicated that the  $\alpha_{1A}$  receptor may also be present in other lower urinary tract tissues, such as urethral smooth muscle (Ford et al. Br. J. Pharmacol., 114, 24P, (1995)).

This invention is directed to dihydropyrimidine compounds which are selective antagonists for cloned human  $\alpha_{1A}$  receptors. This invention is also related to uses of these compounds for lowering intraocular pressure (Zhan, et. al. Ophthalmol. Vis. Sci., 34 Abst. #1133, 928, 1993), inhibiting cholesterol synthesis (D'Eletto and Javitt, J. Cardiovascular Pharmacol., 13 (Suppl. 2) S1-S4, 1989), benign prostatic hyperplasia, impotency (Milne and Wyllie, EP 0 459 666 A2, 1991), sympathetically mediated pain (Campbell, WO 92/14453, 1992), cardiac arrhythmia (Spiers, et. al., J. Cardiovascular Pharmacol., 16, 824-830, 1990) and for the treatment of any disease where antagonism of the  $\alpha_{1A}$  receptor may be useful.

# Summary of the Invention

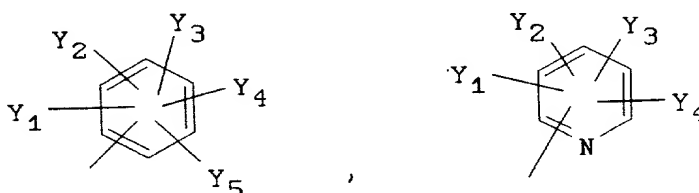
The present invention is directed to compounds having the structure:



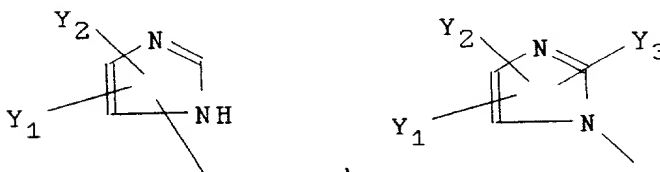
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wherein A is

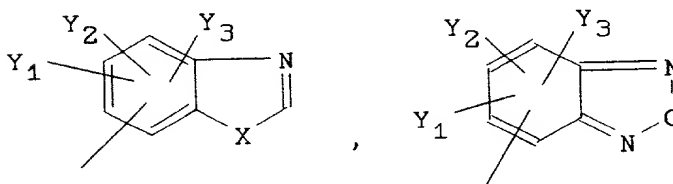
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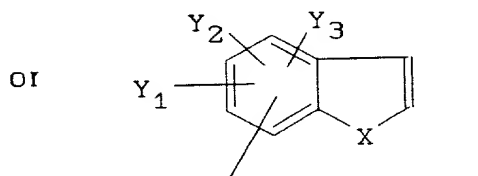
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wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ ,  $Y_4$  and  $Y_5$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; -F, -Cl, -Br, or -I; -NO<sub>2</sub>; -N<sub>3</sub>; -CN; -OR<sub>3</sub>, -OCOR<sub>3</sub>, -COR<sub>3</sub>, -CONHR<sub>3</sub>, -CON(R<sub>3</sub>)<sub>2</sub>, or -COOR<sub>3</sub>; or any two of  $Y_1$ ,  $Y_2$ ,  $Y_3$ ,  $Y_4$  and  $Y_5$  present on adjacent carbon atoms can constitute a methylenedioxy group;

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wherein X is S; O; or NR<sub>3</sub>;

wherein  $R_1$  is -H; -NO<sub>2</sub>; -CN; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; -N(R<sub>3</sub>)<sub>2</sub>; -OR<sub>3</sub>; -(CH<sub>2</sub>)<sub>p</sub>OR<sub>3</sub>; -COR<sub>3</sub>; -CO<sub>2</sub>R<sub>3</sub>; or -CON(R<sub>3</sub>)<sub>2</sub>;

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wherein  $R_2$  is -H; straight chained or branched  $C_1$ - $C_7$  alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;  $C_3$ - $C_{10}$  cycloalkyl- $C_1$ - $C_{10}$ -alkyl,  $C_3$ - $C_{10}$  cycloalkyl- $C_1$ - $C_{10}$ -monofluoroalkyl or  $C_3$ - $C_{10}$  cycloalkyl- $C_1$ - $C_{10}$ -polyfluoroalkyl; -CN; -CH<sub>2</sub>XR<sub>3</sub>, -CH<sub>2</sub>X(CH<sub>2</sub>)<sub>p</sub>NHR<sub>3</sub>, -(CH<sub>2</sub>)<sub>n</sub>NHR<sub>3</sub>, -CH<sub>2</sub>X(CH<sub>2</sub>)<sub>p</sub>N(R<sub>3</sub>)<sub>2</sub>, -CH<sub>2</sub>X(CH<sub>2</sub>)<sub>p</sub>N<sub>3</sub>, or -CH<sub>2</sub>X(CH<sub>2</sub>)<sub>p</sub>NHCXR<sub>7</sub>; or -OR<sub>3</sub>;

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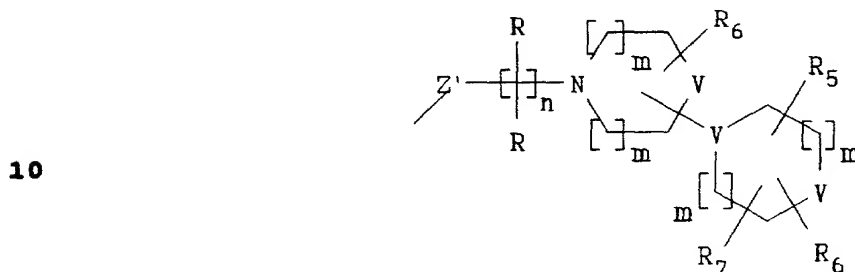
wherein each p is independently an integer from 1 to 7; wherein each n is independently an integer from 0 to 5;

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wherein each  $R_3$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$

alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;

5 wherein R<sub>4</sub> is



wherein Z' is (CH<sub>2</sub>)<sub>o</sub>, CO, (CH<sub>2</sub>)<sub>o</sub>CO, or CO(CH<sub>2</sub>)<sub>o</sub>;

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wherein each V is independently O; S; CH<sub>2</sub>; CR<sub>5</sub>R<sub>7</sub>; C(R<sub>7</sub>)<sub>2</sub>; or NR<sub>7</sub>;

wherein each m is independently an integer from 0 to 3; wherein o is an integer from 1 to 3;

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wherein each R is independently -H; -F; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; -N(R<sub>3</sub>)<sub>2</sub>; -NO<sub>2</sub>; -CN; -CO<sub>2</sub>R<sub>3</sub>; or -OR<sub>3</sub>;

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wherein R<sub>3</sub> and R<sub>7</sub> each independently may be -H; F; Cl; Br; I; -COR<sub>3</sub>; -CO<sub>2</sub>R<sub>3</sub>; -CON(R<sub>3</sub>)<sub>2</sub>; -CN; -NO<sub>2</sub>; -N(R<sub>3</sub>)<sub>2</sub>; -OR<sub>3</sub>; -SR<sub>3</sub>; -(CH<sub>2</sub>)<sub>p</sub>OR<sub>3</sub>; -(CH<sub>2</sub>)<sub>p</sub>SR<sub>3</sub>; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, aminoalkyl, carboxamidoalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl, or C<sub>3</sub>-C<sub>7</sub> cycloalkyl or cycloalkenyl; wherein the alkyl, aminoalkyl, carboxamidoalkyl, alkenyl, alkynyl, cycloalkyl or cycloalkenyl may be substituted with one or more aryl or heteroaryl, wherein the aryl or heteroaryl may be substituted with -F, -Cl, -Br, -I, -NO<sub>2</sub>, -CN, -OR<sub>3</sub>, -SR<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkyl, or carboxamido; aryl or

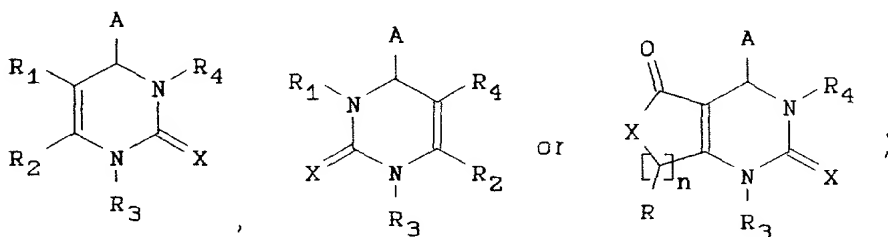
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- heteroaryl, wherein the aryl or heteroaryl may be substituted with one or more -F, -Cl, -Br, -I, COR<sub>3</sub>, CO<sub>2</sub>R<sub>3</sub>, -CON(R<sub>3</sub>)<sub>2</sub>, -CN, -NO<sub>2</sub>, -N(R<sub>3</sub>)<sub>2</sub>, -OR<sub>3</sub>, -SR<sub>3</sub>, (CH<sub>2</sub>)<sub>6</sub>OR<sub>3</sub>, (CH<sub>2</sub>)<sub>6</sub>SR<sub>3</sub>; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl, C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; and
- 10 wherein each R<sub>6</sub> is independently -H; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; or -OR<sub>3</sub>;
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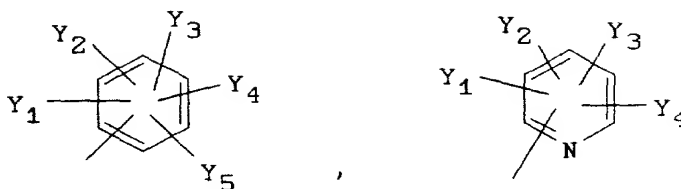
or a pharmaceutically acceptable salt thereof.

- 20 The present invention is also directed to compounds having the structure:

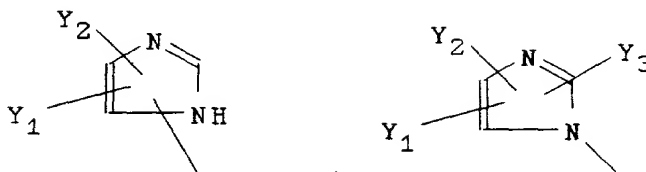


wherein A is

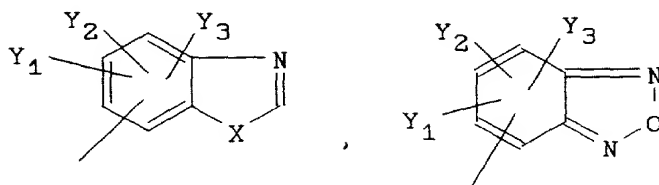
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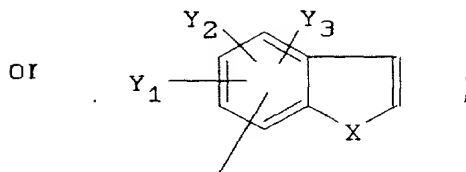
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wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ ,  $Y_4$  and  $Y_5$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; -F, -Cl, -Br, or -I; - $NO_2$ ; - $N_3$ ; -CN; - $OR_3$ , - $OCOR_3$ , - $COR_3$ , - $CONHR_3$ , - $CON(R_3)_2$ , or - $COOR_3$ ; or any two of  $Y_1$ ,  $Y_2$ ,  $Y_3$ ,  $Y_4$  and  $Y_5$  present on adjacent carbon atoms can constitute a methylenedioxy group;

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wherein X is S; O; or  $NR_3$ ;

5 wherein  $R_1$  is -H;  $-NO_2$ ;  $-CN$ ; straight chained or branched  $C_1-C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2-C_7$  alkenyl or alkynyl;  $C_3-C_7$  cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;  $-N(R_3)_2$ ;  $-OR_3$ ;  $-(CH_2)_pOR_3$ ;  $-COR_3$ ;  $-CO_2R_3$ ; or  $-CON(R_3)_2$ ;

10 wherein  $R_2$  is -H; straight chained or branched  $C_1-C_7$  alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2-C_7$  alkenyl or alkynyl;  $C_3-C_7$  cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;  $C_3-C_{10}$  cycloalkyl- $C_1-C_{10}$ -alkyl,  $C_3-C_{10}$  cycloalkyl- $C_1-C_{10}$ -monofluoroalkyl or  $C_3-C_{10}$  cycloalkyl- $C_1-C_{10}$ -polyfluoroalkyl;  $-CN$ ;  $-CH_2XR_3$ ,  $-CH_2X(CH_2)_pNHR_3$ ,  $-(CH_2)_nNHR_3$ ,  $-CH_2X(CH_2)_pN(R_3)_2$ ,  $-CH_2X(CH_2)_pN_3$ , or  $-CH_2X(CH_2)_pNHCXR_7$ ; or  $-OR_3$ ;

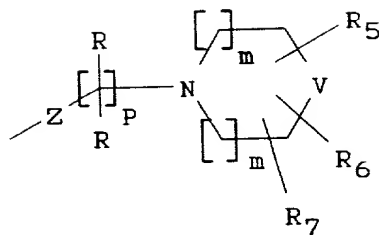
20 wherein each  $p$  is independently an integer from 1 to 7; wherein each  $n$  is independently an integer from 0 to 5;

25 wherein each  $R_3$  is independently -H; straight chained or branched  $C_1-C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2-C_7$  alkenyl or alkynyl;  $C_3-C_7$  cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;

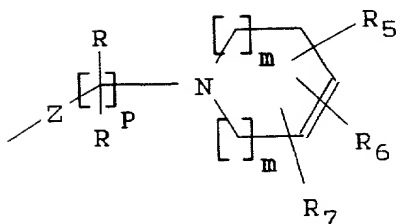
30 wherein  $R_4$  is

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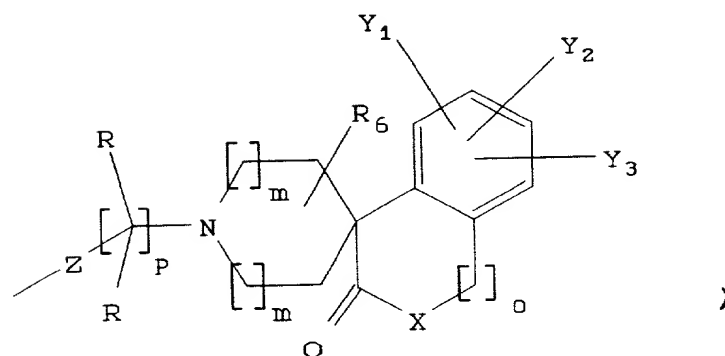
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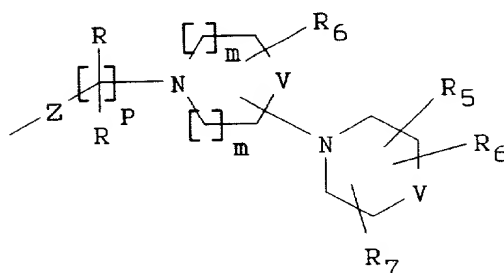


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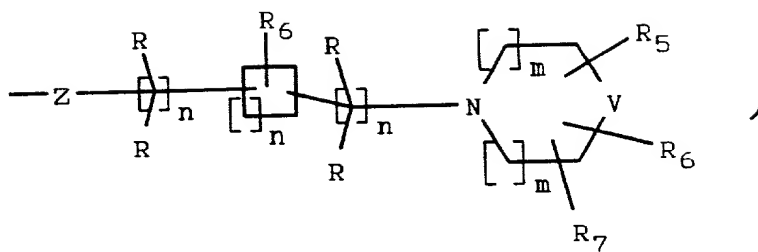


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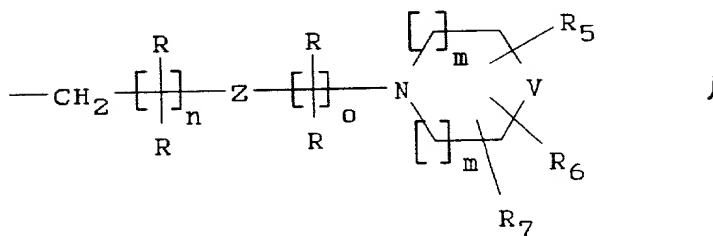
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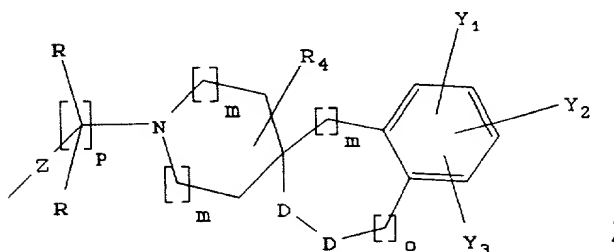


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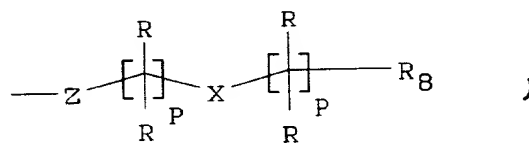
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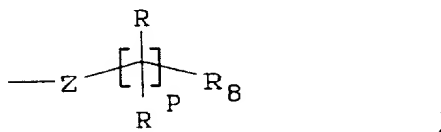


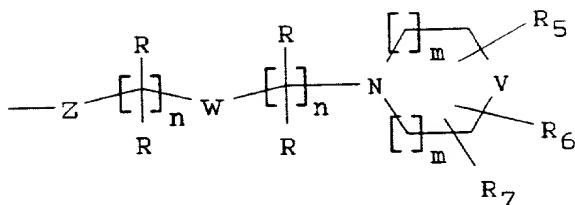
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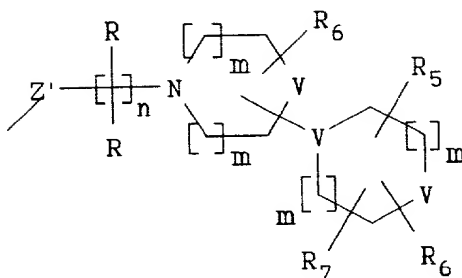


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or



wherein Z is C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; CH<sub>2</sub>; O; CO; CO<sub>2</sub>; CONR<sub>3</sub>; S; SO; SO<sub>2</sub>; or NR<sub>3</sub>;

wherein Z' is (CH<sub>2</sub>)<sub>0</sub>, CO, (CH<sub>2</sub>)<sub>0</sub>CO, or CO(CH<sub>2</sub>)<sub>0</sub>;

wherein each D is independently CH<sub>2</sub>; O; S; NR<sub>3</sub>; CO; or CS;

wherein W is C=O; C=NOR<sub>3</sub>; substituted or unsubstituted phenyl, pyridyl, thiophenyl, furanyl, pyrazinyl, pyrrol, naphthyl, indolyl, imidazolyl, benzfurazanyl, benzfuranyl or benzyimidazolyl, wherein the phenyl, pyridyl, thiophenyl, furanyl, pyrazinyl, pyrrol, naphthyl, indolyl, imidazolyl, benzfurazanyl, benzfuranyl or benzyimidazolyl is substituted with -H, -F, -Cl, -Br, -I, -NO<sub>2</sub>, -CN, straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> monofluoroalkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> polyfluoroalkyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub>

5 alkenyl, straight chained or branched  $C_2-C_7$  alkynyl,  $C_3-C_7$  cycloalkyl,  $C_3-C_7$  monofluorocycloalkyl,  $C_3-C_7$  polyfluorocycloalkyl,  $C_3-C_7$  cycloalkenyl,  $-N(R_3)_2$ ,  $-OR_3$ ,  $-COR_3$ ,  $-CO_2R_3$ , or  $-CON(R_3)_2$ ;

wherein each V is independently O; S;  $CH_2$ ;  $CR_5R_7$ ;  $C(R_7)_2$ ; or  $NR_7$ ;

10 wherein each m is independently an integer from 0 to 3; wherein o is an integer from 1 to 3;

15 wherein each R is independently -H; -F; straight chained or branched  $C_1-C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2-C_7$  alkenyl or alkynyl;  $-N(R_3)_2$ ;  $-NO_2$ ;  $-CN$ ;  $-CO_2R_3$ ; or  $-OR_3$ ;

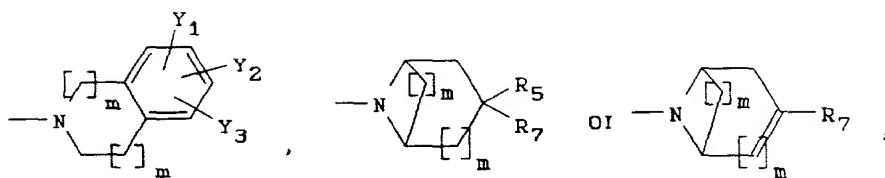
20 wherein  $R_5$  is aryl or heteroaryl substituted with one or more of F; Cl; Br; I;  $COR_3$ ;  $CO_2R_3$ ;  $-CON(R_3)_2$ ;  $CN$ ;  $-NO_2$ ;  $-N(R_3)_2$ ;  $-OR_3$ ,  $-SR_3$ ;  $(CH_2)_oOR_3$ ;  $(CH_2)_oSR_3$ ; straight chained or branched  $C_1-C_7$  alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl, or carboxamidoalkyl; straight chained or branched  $C_2-C_7$  alkenyl,  $C_2-C_7$  alkynyl,  $C_3-C_7$  cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;

30 wherein each  $R_6$  is independently -H; straight chained or branched  $C_1-C_7$  alkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2-C_7$  alkenyl or alkynyl;  $C_3-C_7$  cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; or  $-OR_3$ ;

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wherein  $R_7$  is aryl or heteroaryl substituted with

- one or more of F; Cl; Br; I; COR<sub>3</sub>; CO<sub>2</sub>R<sub>3</sub>; -CON(R<sub>3</sub>)<sub>2</sub>; CN; -NO<sub>2</sub>; -N(R<sub>3</sub>)<sub>2</sub>; -OR<sub>3</sub>, -SR<sub>3</sub>; (CH<sub>2</sub>)<sub>6</sub>OR<sub>3</sub>; (CH<sub>2</sub>)<sub>6</sub>SR<sub>3</sub>; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl, or
- 5 carboxamidoalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl, C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; and
- 10 wherein R<sub>8</sub> is -H; substituted or unsubstituted benzyl, benzoyl, phenyl, pyridyl, thiophenyl, furanyl, pyrazinyl, pyrrol, naphthyl, indolyl, imidazolyl, benzfurazanyl, benzfuranyl, benzimidazolyl or 2-keto-1-benzimidazolyl, or
- 15 wherein the benzyl, benzoyl, phenyl, pyridyl, thiophenyl, furanyl, pyrazinyl, pyrrol, naphthyl, indolyl, imidazolyl, benzfurazanyl, benzfuranyl, benzimidazolyl or 2-keto-1-benzimidazolyl is substituted with -H, -F, -Cl, -Br, -I, -NO<sub>2</sub>, -CN,
- 20 straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> monofluoroalkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> polyfluoroalkyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub>
- 25 monofluorocycloalkyl, C<sub>3</sub>-C<sub>7</sub> polyfluorocycloalkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkenyl, -N(R<sub>3</sub>)<sub>2</sub>, -OR<sub>3</sub>, -COR<sub>3</sub>, -CO<sub>2</sub>R<sub>3</sub>, or -CON(R<sub>3</sub>)<sub>2</sub>; substituted or unsubstituted straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl or polyfluoroalkyl; substituted or unsubstituted
- 30 straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl or cycloalkenyl, wherein the alkyl, monofluoroalkyl, polyfluoroalkyl, alkenyl, alkynyl, cycloalkyl or cycloalkenyl is substituted with -H, phenyl, pyridyl, thiophenyl,
- 35 furanyl, pyrazinyl, pyrrol, naphthyl, indolyl, imidazolyl, benzfurazanyl, benzfuranyl, benzimidazolyl, -N(R<sub>3</sub>)<sub>2</sub>, -NO<sub>2</sub>, -CN, -CO<sub>2</sub>R<sub>3</sub>, -OR<sub>3</sub>;

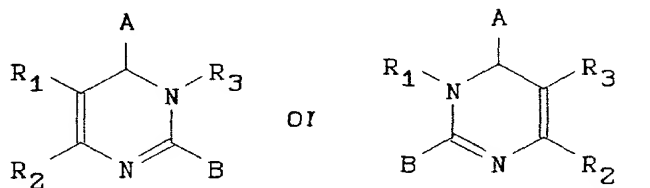


or a pharmaceutically acceptable salt thereof.

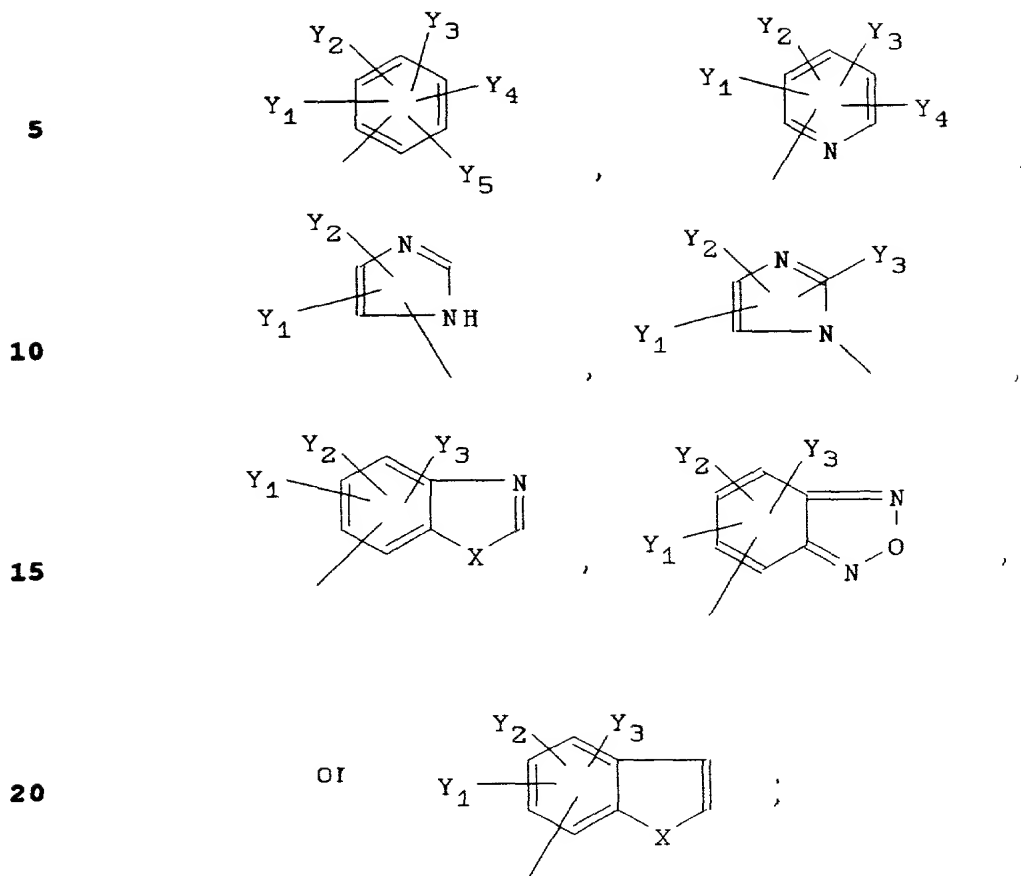
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The present invention is further directed to compounds having the structure:

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wherein A is



25 wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ ,  $Y_4$  and  $Y_5$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; -F, -Cl, -Br, or -I; - $NO_2$ ; - $N_3$ ; -CN; - $OR_4$ , - $OCOR_4$ , - $COR_4$ , - $CONHR_4$ , - $CON(R_4)_2$ , or - $COOR_4$ ; or any two of  $Y_1$ ,  $Y_2$ ,  $Y_3$ ,  $Y_4$  and  $Y_5$  present on adjacent carbon atoms can constitute a methylenedioxy group;

35 wherein X is S; O; or  $NR_4$ ;

wherein B is -H; straight chained or branched  $C_1$ - $C_7$

alkyl, monofluoroalkyl, polyfluoroalkyl, alkoxy or thioalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl; -SCH<sub>2</sub>C<sub>6</sub>H<sub>4</sub>OR<sub>4</sub>; -(CH<sub>2</sub>)<sub>n</sub>C<sub>6</sub>H<sub>5</sub>; -CH<sub>2</sub>X(CH<sub>2</sub>)<sub>p</sub>NHR<sub>4</sub>; -(CH<sub>2</sub>)<sub>n</sub>NHR<sub>4</sub>; or -OR<sub>4</sub>;

5

wherein R<sub>1</sub> is -H; -NO<sub>2</sub>; -CN; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; -N(R<sub>4</sub>)<sub>2</sub>; -OR<sub>4</sub>; -(CH<sub>2</sub>)<sub>p</sub>OR<sub>4</sub>; -COR<sub>4</sub>; -CO<sub>2</sub>R<sub>4</sub>; or -CON(R<sub>4</sub>)<sub>2</sub>;

10

wherein R<sub>2</sub> is -H; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; C<sub>3</sub>-C<sub>10</sub> cycloalkyl-C<sub>1</sub>-C<sub>10</sub>-alkyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl-C<sub>1</sub>-C<sub>10</sub>-monofluoroalkyl or C<sub>3</sub>-C<sub>10</sub> cycloalkyl-C<sub>1</sub>-C<sub>10</sub>-polyfluoroalkyl; -CN; -CH<sub>2</sub>XR<sub>4</sub>, -CH<sub>2</sub>X(CH<sub>2</sub>)<sub>p</sub>NHR<sub>4</sub>, -(CH<sub>2</sub>)<sub>n</sub>NHR<sub>4</sub>, -CH<sub>2</sub>X(CH<sub>2</sub>)<sub>p</sub>N(R<sub>4</sub>)<sub>2</sub>, -CH<sub>2</sub>X(CH<sub>2</sub>)<sub>p</sub>N<sub>3</sub>, or -CH<sub>2</sub>X(CH<sub>2</sub>)<sub>p</sub>NHCXR<sub>7</sub>; or -OR<sub>4</sub>;

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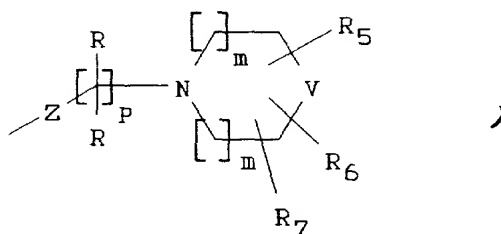
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wherein each p is independently an integer from 1 to 7; wherein each n is independently an integer from 0 to 5;

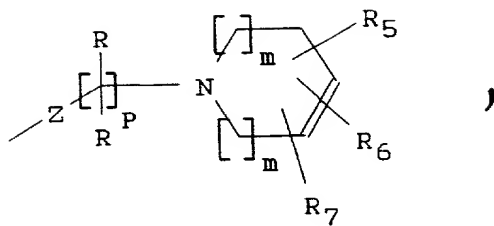
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wherein R<sub>3</sub> is

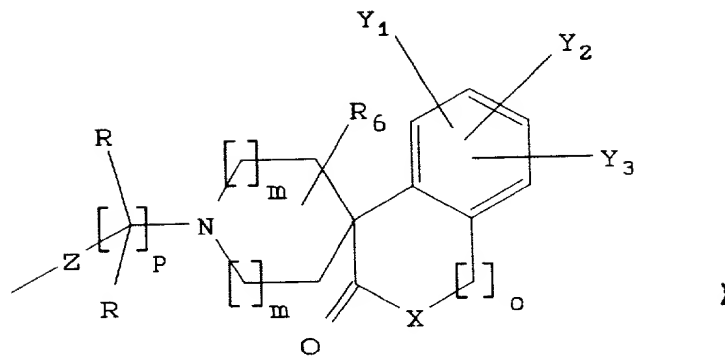


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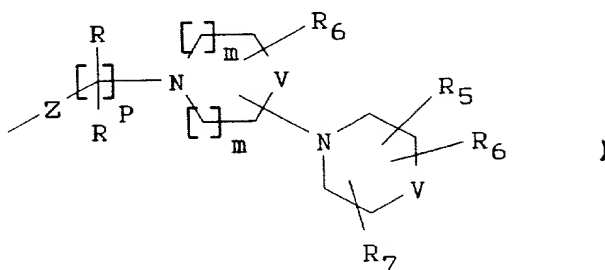


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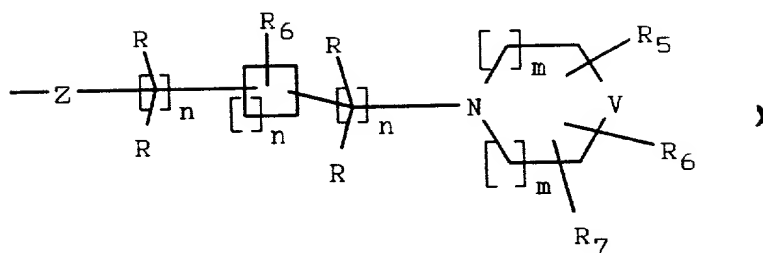
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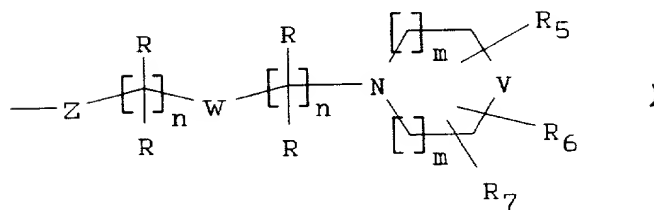
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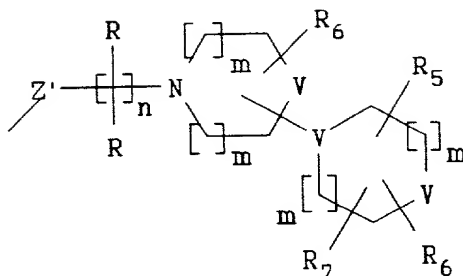
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35



or



wherein Z is C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; CH<sub>2</sub>; O; CO; CO<sub>2</sub>; CONR<sub>4</sub>; S; SO; SO<sub>2</sub>; or NR<sub>4</sub>;

wherein Z' is (CH<sub>2</sub>)<sub>0</sub>, CO, (CH<sub>2</sub>)<sub>0</sub>CO, or CO(CH<sub>2</sub>)<sub>0</sub>;

wherein each D is independently CH<sub>2</sub>; O; S; NR<sub>4</sub>; CO; or CS;

wherein W is C=O; C=NOR<sub>4</sub>; substituted or unsubstituted phenyl, pyridyl, thiophenyl, furanyl, pyrazinyl, pyrrol, naphthyl, indolyl, imidazolyl, benzfurazanyl, benzfuranyl or benzyimidazolyl, wherein the phenyl, pyridyl, thiophenyl, furanyl, pyrazinyl, pyrrol, naphthyl, indolyl, imidazolyl, benzfurazanyl, benzfuranyl or benzyimidazolyl is substituted with -H, -F, -Cl, -Br, -I, -NO<sub>2</sub>, -CN, straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> monofluoroalkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> polyfluoroalkyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub> monofluorocycloalkyl, C<sub>3</sub>-C<sub>7</sub> polyfluorocycloalkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkenyl, -N(R<sub>4</sub>)<sub>2</sub>, -OR<sub>4</sub>, -COR<sub>4</sub>, -CO<sub>2</sub>R<sub>4</sub>, or -CON(R<sub>4</sub>)<sub>2</sub>;

wherein each V is independently O; S; CH<sub>2</sub>; CR<sub>3</sub>R<sub>7</sub>;  
C(R<sub>7</sub>)<sub>2</sub>; or NR<sub>7</sub>;

5 wherein each m is independently an integer from 0  
to 3; wherein o is an integer from 1 to 3;

10 wherein each R is independently -H; -F; straight  
chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl or  
polyfluoroalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub>  
alkenyl or alkynyl; -N(R<sub>4</sub>)<sub>2</sub>; -NO<sub>2</sub>; -CN; -CO<sub>2</sub>R<sub>4</sub>; or  
-OR<sub>4</sub>;

15 wherein each R<sub>4</sub> is independently -H; straight  
chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl or  
polyfluoroalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub>  
alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl,  
monofluorocycloalkyl, polyfluorocycloalkyl or  
cycloalkenyl;

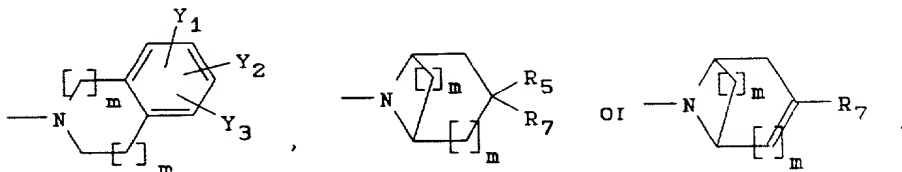
20 wherein R<sub>5</sub> is aryl or heteroaryl substituted with  
one or more of F; Cl; Br; I; COR<sub>3</sub>; CO<sub>2</sub>R<sub>3</sub>; -CON(R<sub>3</sub>)<sub>2</sub>;  
CN; -NO<sub>2</sub>; -N(R<sub>3</sub>)<sub>2</sub>; -OR<sub>3</sub>, -SR<sub>3</sub>; (CH<sub>2</sub>)<sub>o</sub>OR<sub>3</sub>; (CH<sub>2</sub>)<sub>o</sub>SR<sub>3</sub>;  
straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl,  
monofluoroalkyl, polyfluoroalkyl, aminoalkyl, or  
25 carboxamidoalkyl; straight chained or branched  
C<sub>2</sub>-C<sub>7</sub> alkenyl, C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl,  
monofluorocycloalkyl, polyfluorocycloalkyl or  
cycloalkenyl;

30 wherein each R<sub>6</sub> is independently -H; straight  
chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, hydroxyalkyl,  
aminoalkyl, alkoxyalkyl, monofluoroalkyl or  
polyfluoroalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub>  
alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl,  
35 monofluorocycloalkyl, polyfluorocycloalkyl or  
cycloalkenyl; or -OR<sub>4</sub>;

wherein  $R_7$  is aryl or heteroaryl substituted with one or more of F; Cl; Br; I;  $\text{COR}_3$ ;  $\text{CO}_2\text{R}_3$ ;  $-\text{CON}(\text{R}_3)_2$ ; CN;  $-\text{NO}_2$ ;  $-\text{N}(\text{R}_3)_2$ ;  $-\text{OR}_3$ ,  $-\text{SR}_3$ ;  $(\text{CH}_2)_6\text{OR}_3$ ;  $(\text{CH}_2)_6\text{SR}_3$ ; straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl, or carboxamidoalkyl; straight chained or branched  $\text{C}_2\text{-C}_7$  alkenyl,  $\text{C}_2\text{-C}_7$  alkynyl,  $\text{C}_3\text{-C}_7$  cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; and

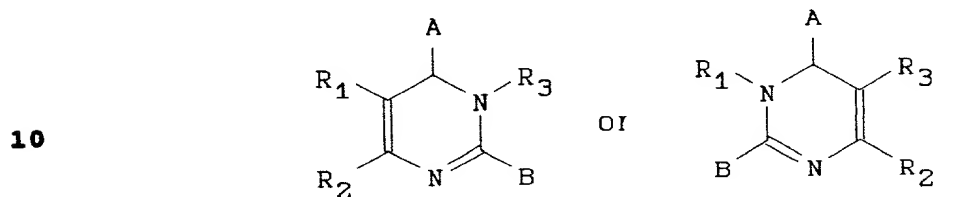
wherein  $R_8$  is -H; substituted or unsubstituted benzyl, benzoyl, phenyl, pyridyl, thiophenyl, furanyl, pyrazinyl, pyrrolyl, naphthyl, indolyl, imidazolyl, benzfurazanyl, benzfuranyl, benzimidazolyl or 2-keto-1-benzimidazolyl, wherein the benzyl, benzoyl, phenyl, pyridyl, thiophenyl, furanyl, pyrazinyl, pyrrolyl, naphthyl, indolyl, imidazolyl, benzfurazanyl, benzfuranyl, benzimidazolyl or 2-keto-1-benzimidazolyl is substituted with -H, -F, -Cl, -Br, -I,  $-\text{NO}_2$ , -CN, straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl, straight chained or branched  $\text{C}_1\text{-C}_7$  monofluoroalkyl, straight chained or branched  $\text{C}_1\text{-C}_7$  polyfluoroalkyl, straight chained or branched  $\text{C}_2\text{-C}_7$  alkenyl, straight chained or branched  $\text{C}_2\text{-C}_7$  alkynyl,  $\text{C}_3\text{-C}_7$  cycloalkyl,  $\text{C}_3\text{-C}_7$  monofluorocycloalkyl,  $\text{C}_3\text{-C}_7$  polyfluorocycloalkyl,  $\text{C}_3\text{-C}_7$  cycloalkenyl,  $-\text{N}(\text{R}_4)_2$ ,  $-\text{OR}_4$ ,  $-\text{COR}_4$ ,  $-\text{CO}_2\text{R}_4$ , or  $-\text{CON}(\text{R}_4)_2$ ; substituted or unsubstituted straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; substituted or unsubstituted straight chained or branched  $\text{C}_2\text{-C}_7$  alkenyl or alkynyl;  $\text{C}_3\text{-C}_7$  cycloalkyl or cycloalkenyl, wherein the alkyl, monofluoroalkyl, polyfluoroalkyl, alkenyl, alkynyl, cycloalkyl or cycloalkenyl is substituted with -H, phenyl, pyridyl, thiophenyl, furanyl, pyrazinyl, pyrrolyl, naphthyl, indolyl, imidazolyl, benzfurazanyl, benzfuranyl,

benzimidazolyl,  $-N(R_4)_2$ ,  $-NO_2$ ,  $-CN$ ,  $-CO_2R_4$ ,  $-OR_4$ ;



or a pharmaceutically acceptable salt thereof.

5 The present invention is also directed to compounds having the structure:



wherein A is

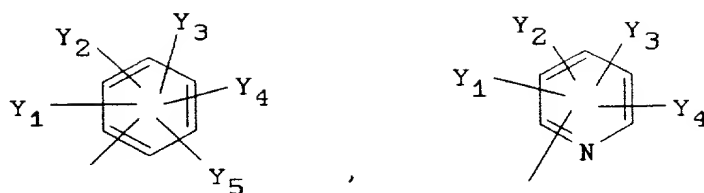
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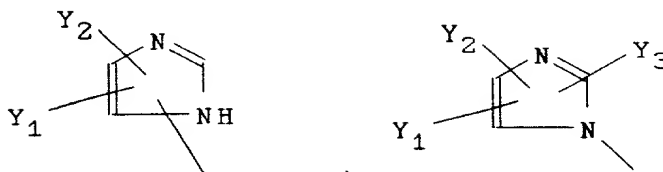
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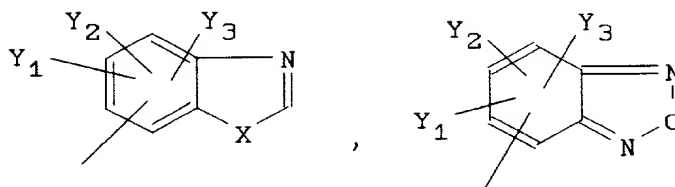
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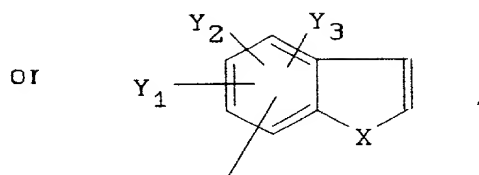
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wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ ,  $Y_4$  and  $Y_5$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; -F, -Cl, -Br, or -I; - $NO_2$ ; - $N_3$ ; -CN; - $OR_4$ , - $OCOR_4$ , - $COR_4$ , - $CONHR_4$ , - $CON(R_4)_2$ , or - $COOR_4$ ; or any two of  $Y_1$ ,  $Y_2$ ,  $Y_3$ ,  $Y_4$  and  $Y_5$  present on adjacent carbon atoms can constitute a methylenedioxy group;

35

wherein X is S; O; or  $NR_4$ ;

wherein B is -H; straight chained or branched  $C_1$ - $C_7$

alkyl, monofluoroalkyl, polyfluoroalkyl, alkoxy or thioalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl; -SCH<sub>2</sub>C<sub>6</sub>H<sub>4</sub>OR<sub>4</sub>; -(CH<sub>2</sub>)<sub>n</sub>C<sub>6</sub>H<sub>5</sub>; -CH<sub>2</sub>X(CH<sub>2</sub>)<sub>n</sub>NHR<sub>4</sub>; -(CH<sub>2</sub>)<sub>n</sub>NHR<sub>4</sub>; or -OR<sub>4</sub>;

5

wherein R<sub>1</sub> is -H; -NO<sub>2</sub>; -CN; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; -N(R<sub>4</sub>)<sub>2</sub>; -OR<sub>4</sub>; -(CH<sub>2</sub>)<sub>p</sub>OR<sub>4</sub>; -COR<sub>4</sub>; -CO<sub>2</sub>R<sub>4</sub>; or -CON(R<sub>4</sub>)<sub>2</sub>;

10

wherein R<sub>2</sub> is -H; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; C<sub>3</sub>-C<sub>10</sub> cycloalkyl-C<sub>1</sub>-C<sub>10</sub>-alkyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl-C<sub>1</sub>-C<sub>10</sub>-monofluoroalkyl or C<sub>3</sub>-C<sub>10</sub> cycloalkyl-C<sub>1</sub>-C<sub>10</sub>-polyfluoroalkyl; -CN; -CH<sub>2</sub>XR<sub>4</sub>, -CH<sub>2</sub>X(CH<sub>2</sub>)<sub>p</sub>NHR<sub>4</sub>, -(CH<sub>2</sub>)<sub>n</sub>NHR<sub>4</sub>, -CH<sub>2</sub>X(CH<sub>2</sub>)<sub>p</sub>N(R<sub>4</sub>)<sub>2</sub>, -CH<sub>2</sub>X(CH<sub>2</sub>)<sub>p</sub>N<sub>3</sub>, or -CH<sub>2</sub>X(CH<sub>2</sub>)<sub>p</sub>NHCXR<sub>7</sub>; or -OR<sub>4</sub>;

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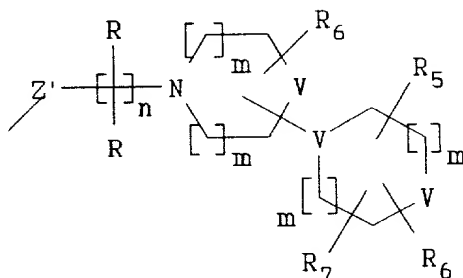
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wherein each p is independently an integer from 1 to 7; wherein each n is independently an integer from 0 to 5;

wherein R<sub>3</sub> is

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35

wherein  $Z'$  is  $(CH_2)_o$ ,  $CO$ ,  $(CH_2)_oCO$ , or  $CO(CH_2)_o$ ;

5

wherein each  $V$  is independently  $O$ ;  $S$ ;  $CH_2$ ;  $CR_5R_7$ ;  
 $C(R_7)_2$ ; or  $NR_7$ ;

10

wherein each  $m$  is independently an integer from 0  
to 3; wherein  $o$  is an integer from 1 to 3;

15

wherein each  $R$  is independently  $-H$ ;  $-F$ ; straight  
chained or branched  $C_1-C_7$  alkyl, monofluoroalkyl or  
polyfluoroalkyl; straight chained or branched  $C_2-C_7$   
alkenyl or alkynyl;  $-N(R_4)_2$ ;  $-NO_2$ ;  $-CN$ ;  $-CO_2R_4$ ; or  
 $-OR_4$ ;

20

wherein each  $R_4$  is independently  $-H$ ; straight  
chained or branched  $C_1-C_7$  alkyl, monofluoroalkyl or  
polyfluoroalkyl; straight chained or branched  $C_2-C_7$   
alkenyl or alkynyl;  $C_3-C_7$  cycloalkyl,  
monofluorocycloalkyl, polyfluorocycloalkyl or  
cycloalkenyl;

25

wherein  $R_5$  and  $R_7$  each independently may be  $-H$ ;  $F$ ;  
 $Cl$ ;  $Br$ ;  $I$ ;  $-COR_3$ ;  $-CO_2R_3$ ;  $-CON(R_3)_2$ ;  $-CN$ ;  $-NO_2$ ;  
 $-N(R_3)_2$ ;  $-OR_3$ ;  $-SR_3$ ;  $-(CH_2)_pOR_3$ ;  $-(CH_2)_pSR_3$ ; straight  
chained or branched  $C_1-C_7$  alkyl, aminoalkyl,  
carboxamidoalkyl; straight chained or branched  
30  $C_2-C_7$  alkenyl or alkynyl, or  $C_3-C_7$  cycloalkyl or  
cycloalkenyl; wherein the alkyl, aminoalkyl,  
carboxamidoalkyl, alkenyl, alkynyl, cycloalkyl or  
cycloalkenyl may be substituted with one or more  
aryl or heteroaryl, wherein the aryl or heteroaryl  
35 may be substituted with  $-F$ ,  $-Cl$ ,  $-Br$ ,  $-I$ ,  $-NO_2$ ,  $-$   
 $CN$ ,  $-OR_3$ ,  $-SR_3$ ,  $C_1-C_3$  alkyl, or carboxamido; aryl or  
heteroaryl, wherein the aryl or heteroaryl may be



substituted with one or more -F, -Cl, -Br,  
-I,  $\text{COR}_3$ ,  $\text{CO}_2\text{R}_3$ ,  $-\text{CON}(\text{R}_3)_2$ , -CN,  $-\text{NO}_2$ ,  $-\text{N}(\text{R}_3)_2$ ,  $-\text{OR}_3$ ,  
- $\text{SR}_3$ ,  $(\text{CH}_2)_6\text{OR}_3$ ,  $(\text{CH}_2)_6\text{SR}_3$ ; straight chained or  
branched  $\text{C}_1\text{-C}_7$  alkyl, monofluoroalkyl or  
polyfluoroalkyl; straight chained or branched  $\text{C}_2\text{-C}_7$   
alkenyl,  $\text{C}_2\text{-C}_7$  alkynyl,  $\text{C}_3\text{-C}_7$  cycloalkyl,  
monofluorocycloalkyl, polyfluorocycloalkyl or  
cycloalkenyl; and

wherein each  $\text{R}_6$  is independently -H; straight  
chained or branched  $\text{C}_1\text{-C}_7$  alkyl, hydroxyalkyl,  
aminoalkyl, alkoxyalkyl, monofluoroalkyl or  
polyfluoroalkyl; straight chained or branched  $\text{C}_2\text{-C}_7$   
alkenyl or alkynyl;  $\text{C}_3\text{-C}_7$  cycloalkyl,  
monofluorocycloalkyl, polyfluorocycloalkyl or  
cycloalkenyl; or  $-\text{OR}_4$ ;

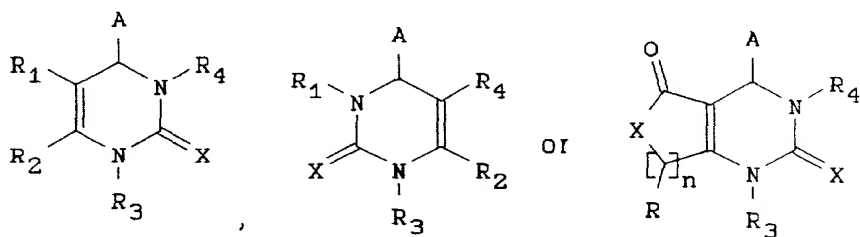
or a pharmaceutically acceptable salt thereof.

This invention is also related to uses of these  
compounds for lowering intraocular pressure, inhibiting  
cholesterol synthesis, relaxing lower urinary tract  
tissue, the treatment of benign prostatic hyperplasia,  
impotency, cardiac arrhythmia and for the treatment of  
any disease where antagonism of the  $\alpha_{1A}$  receptor may be  
useful. The invention further provides a  
pharmaceutical composition comprising a therapeutically  
effective amount of the above-defined compounds and a  
pharmaceutically acceptable carrier.



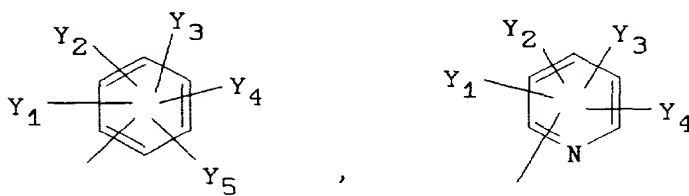
Detailed Description of the Invention

The present invention is directed to compounds having the structure:

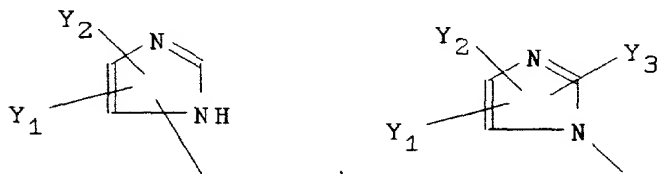


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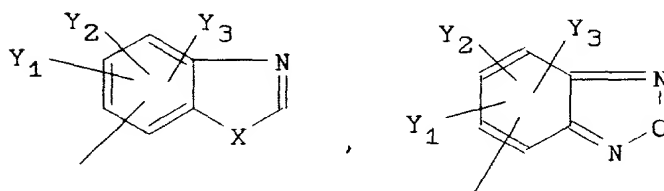
wherein A is



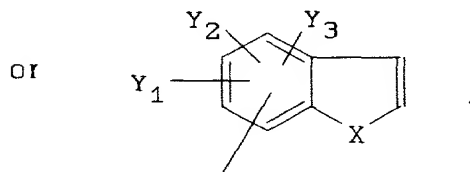
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wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ ,  $Y_4$  and  $Y_5$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; -F, -Cl, -Br, or -I; - $NO_2$ ; - $N_3$ ; -CN; - $OR_3$ , - $OCOR_3$ , - $COR_3$ , - $CONHR_3$ , - $CON(R_3)_2$ , or - $COOR_3$ ; or any two of  $Y_1$ ,  $Y_2$ ,  $Y_3$ ,  $Y_4$  and  $Y_5$  present on adjacent carbon atoms can constitute a methylenedioxy group;

wherein X is S; O; or  $NR_3$ ;

wherein  $R_1$  is -H; - $NO_2$ ; -CN; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; - $N(R_3)_2$ ; - $OR_3$ ; - $(CH_2)_pOR_3$ ; - $COR_3$ ; - $CO_2R_3$ ; or - $CON(R_3)_2$ ;

wherein  $R_2$  is -H; straight chained or branched  $C_1$ - $C_7$  alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;  $C_3$ - $C_{10}$  cycloalkyl- $C_1$ - $C_{10}$ -alkyl,  $C_3$ - $C_{10}$  cycloalkyl- $C_1$ - $C_{10}$ -monofluoroalkyl or  $C_3$ - $C_{10}$  cycloalkyl- $C_1$ - $C_{10}$ -polyfluoroalkyl; -CN; - $CH_2XR_3$ , - $CH_2X(CH_2)_pNHR_3$ , - $(CH_2)_nNHR_3$ , - $CH_2X(CH_2)_pN(R_3)_2$ , - $CH_2X(CH_2)_pN_3$ , or - $CH_2X(CH_2)_pNHCXR_7$ ; or - $OR_3$ ;

wherein each p is independently an integer from 1 to 7; wherein each n is independently an integer from 0 to 5;

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carboxamidoalkyl, alkenyl, alkynyl, cycloalkyl or cycloalkenyl may be substituted with one or more aryl or heteroaryl, wherein the aryl or heteroaryl may be substituted with -F, -Cl, -Br, -I, -NO<sub>2</sub>, -CN, -OR<sub>3</sub>, -SR<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkyl, or carboxamido; aryl or heteroaryl, wherein the aryl or heteroaryl may be substituted with one or more -F, -Cl, -Br, -I, COR<sub>3</sub>, CO<sub>2</sub>R<sub>3</sub>, -CON(R<sub>3</sub>)<sub>2</sub>, -CN, -NO<sub>2</sub>, -N(R<sub>3</sub>)<sub>2</sub>, -OR<sub>3</sub>, -SR<sub>3</sub>, (CH<sub>2</sub>)<sub>6</sub>OR<sub>3</sub>, (CH<sub>2</sub>)<sub>6</sub>SR<sub>3</sub>; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl, C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; and

wherein each R<sub>6</sub> is independently -H; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; or -OR<sub>3</sub>;

or a pharmaceutically acceptable salt thereof.

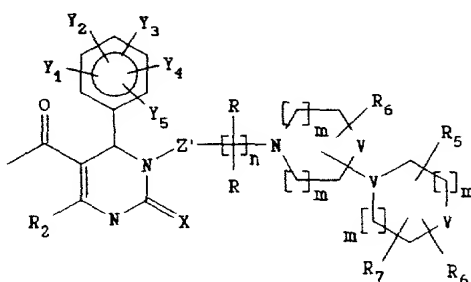
The invention further provides for the (+) enantiomer of any of the compounds described herein which is a cis isomer or a trans isomer. The invention also provides for the (-) enantiomer of any of the compounds described herein which is a cis or a trans isomer.

The compounds of the present invention are preferably at least 80% pure, more preferably 90% pure, and most preferably 95% pure.

Ten fold selectivity differences are a minimum, but one skilled in the art will appreciate that compounds can

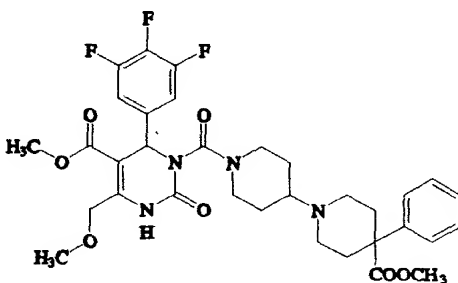
be found that collectively have almost infinitely variable selective profiles. Compounds collectively having all possible combinations of selectivities are intended within the scope of this invention, provided  
5 that each of these compounds has at least ten-fold greater affinity for the  $\alpha_{1A}$  receptor over the  $\alpha_{1B}$  and/or  $\alpha_{1D}$  receptors.

In one embodiment of the present invention the compound  
10 has the structure:



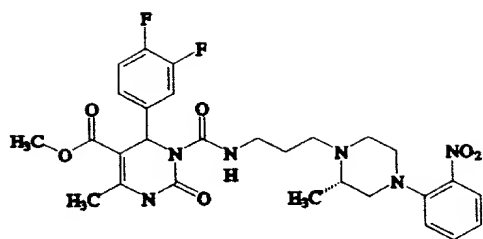
In one embodiment of the present invention Z' is CO and  
20 n is 0.

In another embodiment of the present invention the  
25 compounds have the structure:

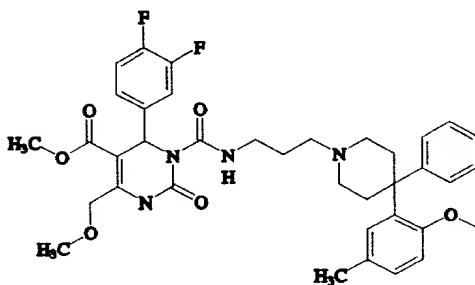


The invention provides for compounds having the  
35 following structures:

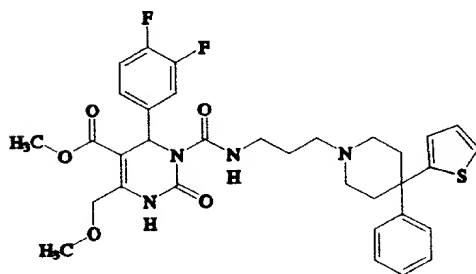
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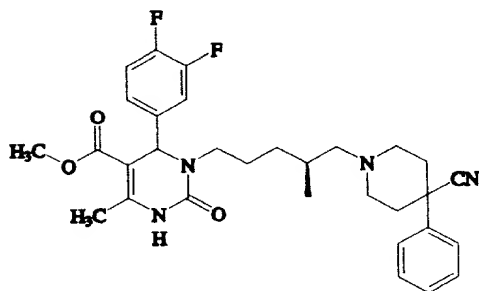


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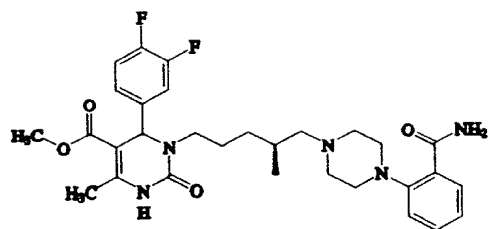


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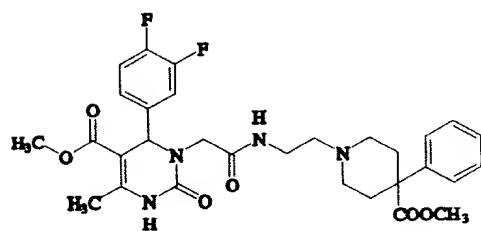
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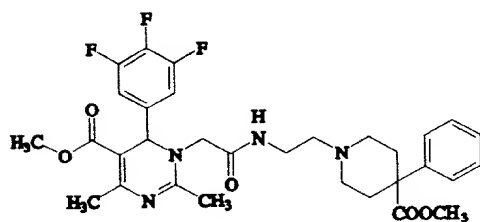
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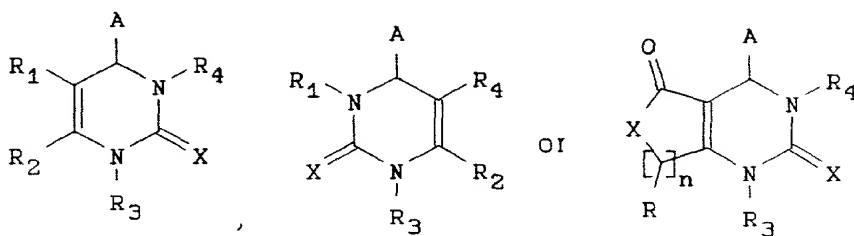
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and

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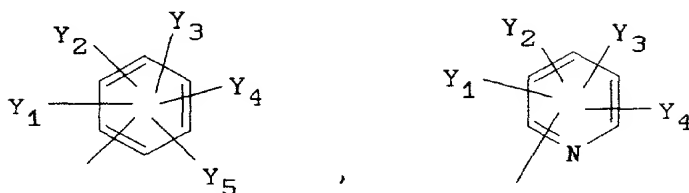


The present invention is also directed to compounds having the structure:

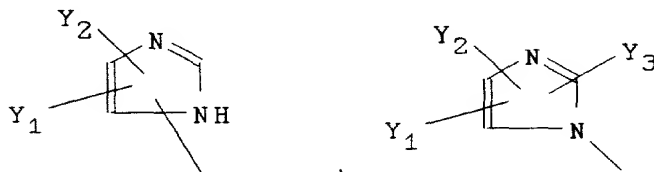


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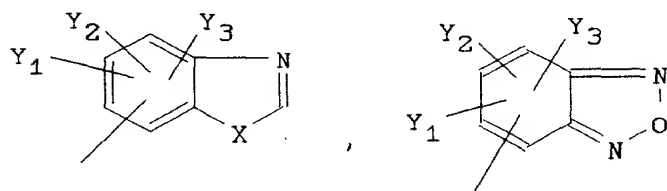
wherein A is



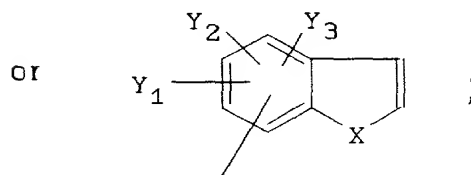
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wherein each of Y<sub>1</sub>, Y<sub>2</sub>, Y<sub>3</sub>, Y<sub>4</sub> and Y<sub>5</sub> is independently -H; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl or polyfluoroalkyl;

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straight chained or branched  $C_2-C_7$  alkenyl or alkynyl;  $C_3-C_7$  cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; -F, -Cl, -Br, or -I;  $-NO_2$ ;  $-N_3$ ; -CN;  $-OR_3$ ,  $-OCOR_3$ ,  $-COR_3$ ,  
5  $-CONHR_3$ ,  $-CON(R_3)_2$ , or  $-COOR_3$ ; or any two of  $Y_1$ ,  $Y_2$ ,  $Y_3$ ,  $Y_4$  and  $Y_5$  present on adjacent carbon atoms can constitute a methylenedioxy group;

wherein X is S; O; or  $NR_3$ ;

10

wherein  $R_1$  is -H;  $-NO_2$ ; -CN; straight chained or branched  $C_1-C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2-C_7$  alkenyl or alkynyl;  $C_3-C_7$  cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;  $-N(R_3)_2$ ;  $-OR_3$ ;  $-(CH_2)_pOR_3$ ;  $-COR_3$ ;  $-CO_2R_3$ ;  
15 or  $-CON(R_3)_2$ ;

15

wherein  $R_2$  is -H; straight chained or branched  $C_1-C_7$  alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2-C_7$  alkenyl or alkynyl;  $C_3-C_7$  cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;  $C_3-C_{10}$  cycloalkyl- $C_1-C_{10}$ -alkyl,  $C_3-C_{10}$  cycloalkyl- $C_1-C_{10}$ -monofluoroalkyl or  $C_3-C_{10}$  cycloalkyl- $C_1-C_{10}$ -polyfluoroalkyl; -CN;  $-CH_2XR_3$ ,  $-CH_2X(CH_2)_pNHR_3$ ,  
20  $-(CH_2)_nNHR_3$ ,  $-CH_2X(CH_2)_pN(R_3)_2$ ,  $-CH_2X(CH_2)_pN_3$ , or  $-CH_2X(CH_2)_pNHCXR_7$ ; or  $-OR_3$ ;

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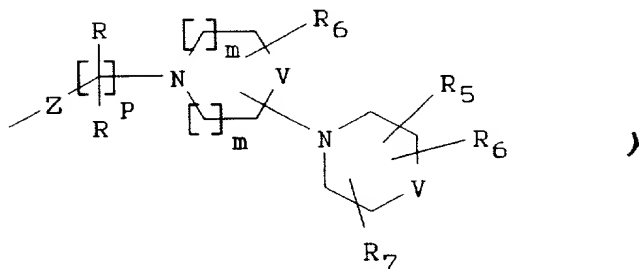
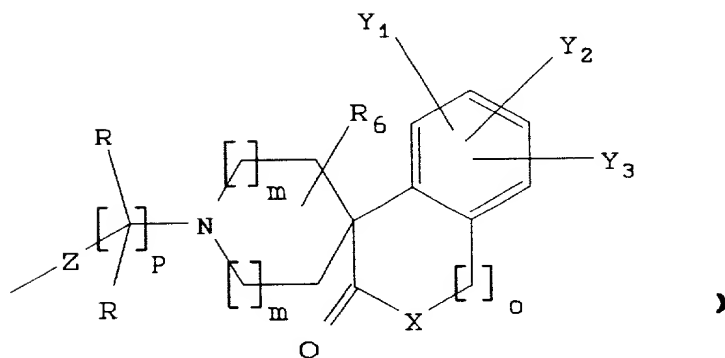
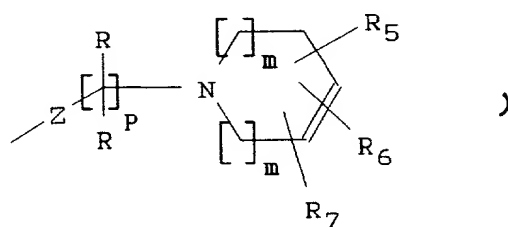
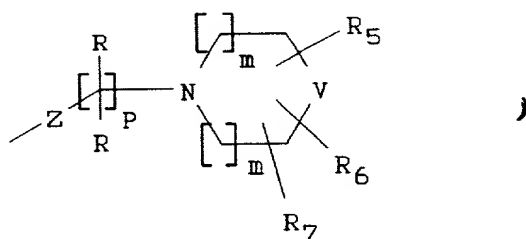
wherein each p is independently an integer from 1 to 7; wherein each n is independently an integer from 0 to 5;

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wherein each  $R_3$  is independently -H; straight chained or branched  $C_1-C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2-C_7$

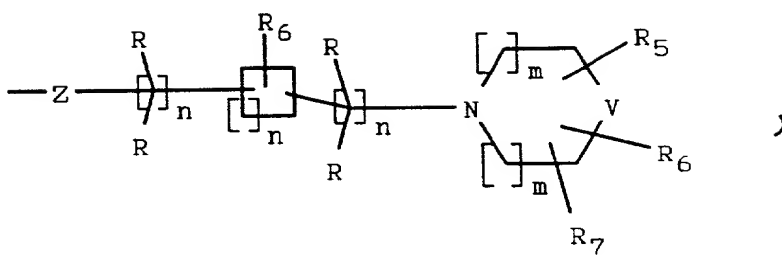
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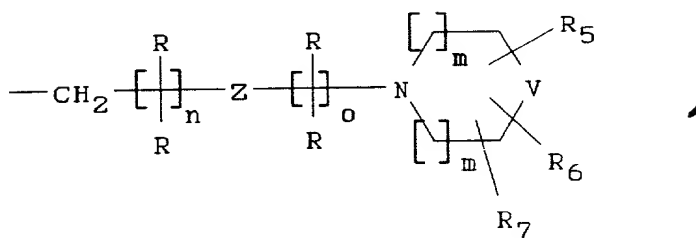


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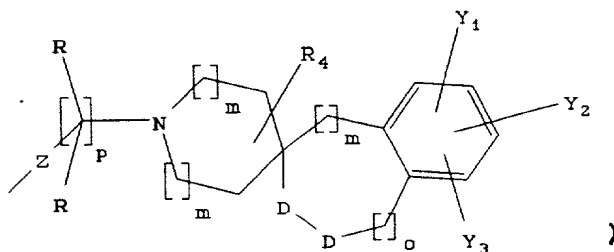


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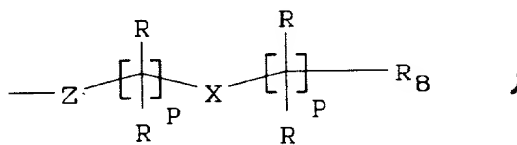


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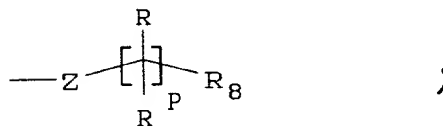
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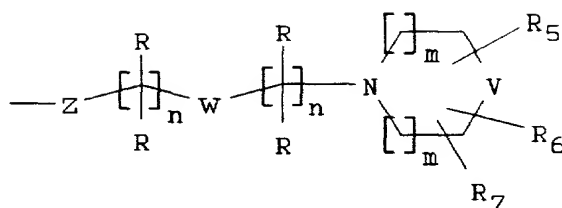
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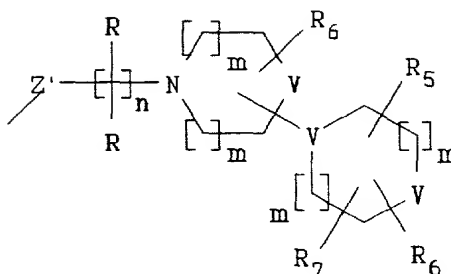
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or



wherein Z is C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; CH<sub>2</sub>; O; CO; CO<sub>2</sub>; CONR<sub>3</sub>; S; SO; SO<sub>2</sub>; or NR<sub>3</sub>;

wherein Z' is (CH<sub>2</sub>)<sub>o</sub>, CO, (CH<sub>2</sub>)<sub>o</sub>CO, or CO(CH<sub>2</sub>)<sub>o</sub>;

wherein each D is independently CH<sub>2</sub>; O; S; NR<sub>3</sub>; CO; or CS;

wherein W is C=O; C=NOR<sub>3</sub>; substituted or unsubstituted phenyl, pyridyl, thiophenyl, furanyl, pyrazinyl, pyrrol, naphthyl, indolyl, imidazolyl, benzfurazanyl, benzfuranyl or benzyimidazolyl, wherein the phenyl, pyridyl, thiophenyl, furanyl, pyrazinyl, pyrrol, naphthyl, indolyl, imidazolyl, benzfurazanyl, benzfuranyl or benzyimidazolyl is substituted with -H, -F, -Cl, -Br, -I, -NO<sub>2</sub>, -CN, straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> monofluoroalkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub> polyfluoroalkyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub>

alkenyl, straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>3</sub>-C<sub>7</sub> monofluorocycloalkyl, C<sub>3</sub>-C<sub>7</sub> polyfluorocycloalkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkenyl, -N(R<sub>3</sub>)<sub>2</sub>, -OR<sub>3</sub>, -COR<sub>3</sub>, -CO<sub>2</sub>R<sub>3</sub>, or -CON(R<sub>3</sub>)<sub>2</sub>;

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wherein each V is independently O; S; CH<sub>2</sub>; CR<sub>5</sub>R<sub>7</sub>; C(R<sub>7</sub>)<sub>2</sub>; or NR<sub>7</sub>; provided that when V is CR<sub>5</sub>R<sub>7</sub> the remaining carbons on the ring may only be substituted with R<sub>6</sub>;

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wherein each m is independently an integer from 0 to 3; wherein o is an integer from 1 to 3;

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wherein each R is independently -H; -F; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; -N(R<sub>3</sub>)<sub>2</sub>; -NO<sub>2</sub>; -CN; -CO<sub>2</sub>R<sub>3</sub>; or -OR<sub>3</sub>;

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wherein R<sub>5</sub> is aryl or heteroaryl substituted with one or more of F; Cl; Br; I; COR<sub>3</sub>; CO<sub>2</sub>R<sub>3</sub>; -CON(R<sub>3</sub>)<sub>2</sub>; CN; -NO<sub>2</sub>; -N(R<sub>3</sub>)<sub>2</sub>; -OR<sub>3</sub>, -SR<sub>3</sub>; (CH<sub>2</sub>)<sub>o</sub>OR<sub>3</sub>; (CH<sub>2</sub>)<sub>o</sub>SR<sub>3</sub>; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl, or carboxamidoalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl, C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;

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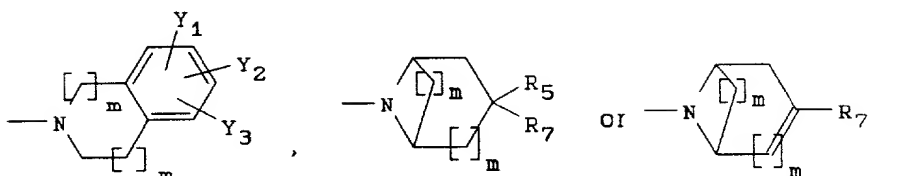
wherein each R<sub>6</sub> is independently -H; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; or -OR<sub>3</sub>;

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- wherein  $R_7$  is aryl or heteroaryl substituted with one or more of F; Cl; Br; I;  $\text{COR}_3$ ;  $\text{CO}_2\text{R}_3$ ;  $-\text{CON}(\text{R}_3)_2$ ; CN;  $-\text{NO}_2$ ;  $-\text{N}(\text{R}_3)_2$ ;  $-\text{OR}_3$ ,  $-\text{SR}_3$ ;  $(\text{CH}_2)_6\text{OR}_3$ ;  $(\text{CH}_2)_6\text{SR}_3$ ; straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl, 5 monofluoroalkyl, polyfluoroalkyl, aminoalkyl, or carboxamidoalkyl; straight chained or branched  $\text{C}_2\text{-C}_7$  alkenyl,  $\text{C}_2\text{-C}_7$  alkynyl,  $\text{C}_3\text{-C}_7$  cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; and
- 10 wherein  $R_8$  is -H; substituted or unsubstituted benzyl, benzoyl, phenyl, pyridyl, thiophenyl, furanyl, pyrazinyl, pyrrolyl, naphthyl, indolyl, imidazolyl, benzfurazanyl, benzfuranyl, 15 benzimidazolyl or 2-keto-1-benzimidazolyl, wherein the benzyl, benzoyl, phenyl, pyridyl, thiophenyl, furanyl, pyrazinyl, pyrrolyl, naphthyl, indolyl, imidazolyl, benzfurazanyl, benzfuranyl, benzimidazolyl or 2-keto-1-benzimidazolyl is 20 substituted with -H, -F, -Cl, -Br, -I,  $-\text{NO}_2$ , -CN, straight chained or branched  $\text{C}_1\text{-C}_7$  alkyl, straight chained or branched  $\text{C}_1\text{-C}_7$  monofluoroalkyl, straight chained or branched  $\text{C}_1\text{-C}_7$  polyfluoroalkyl, straight 25 chained or branched  $\text{C}_2\text{-C}_7$  alkenyl, straight chained or branched  $\text{C}_2\text{-C}_7$  alkynyl,  $\text{C}_3\text{-C}_7$  cycloalkyl,  $\text{C}_3\text{-C}_7$  monofluorocycloalkyl,  $\text{C}_3\text{-C}_7$  polyfluorocycloalkyl,  $\text{C}_3\text{-C}_7$  cycloalkenyl,  $-\text{N}(\text{R}_3)_2$ ,  $-\text{OR}_3$ ,  $-\text{COR}_3$ ,  $-\text{CO}_2\text{R}_3$ , or  $-\text{CON}(\text{R}_3)_2$ ; substituted or unsubstituted straight 30 chained or branched  $\text{C}_1\text{-C}_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; substituted or unsubstituted straight chained or branched  $\text{C}_2\text{-C}_7$  alkenyl or alkynyl;  $\text{C}_3\text{-C}_7$  cycloalkyl or cycloalkenyl, wherein the alkyl, monofluoroalkyl, polyfluoroalkyl, 35 alkenyl, alkynyl, cycloalkyl or cycloalkenyl is substituted with -H, phenyl, pyridyl, thiophenyl, furanyl, pyrazinyl, pyrrolyl, naphthyl, indolyl, imidazolyl, benzfurazanyl, benzfuranyl,



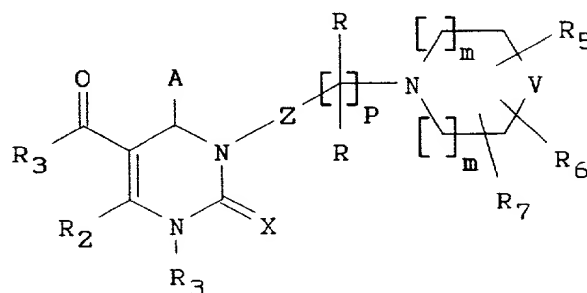
benzimidazolyl,  $-N(R_3)_2$ ,  $-NO_2$ ,  $-CN$ ,  $-CO_2R_3$ ,  $-OR_3$ ;



5 or a pharmaceutically acceptable salt thereof.

In one embodiment of the present invention the compounds have the following structure:

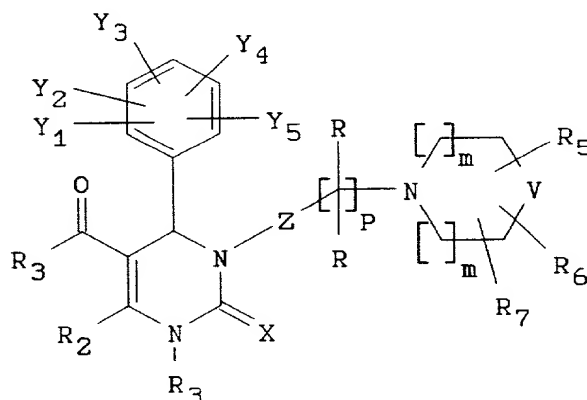
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In a further embodiment of the present invention the compounds have the structure:

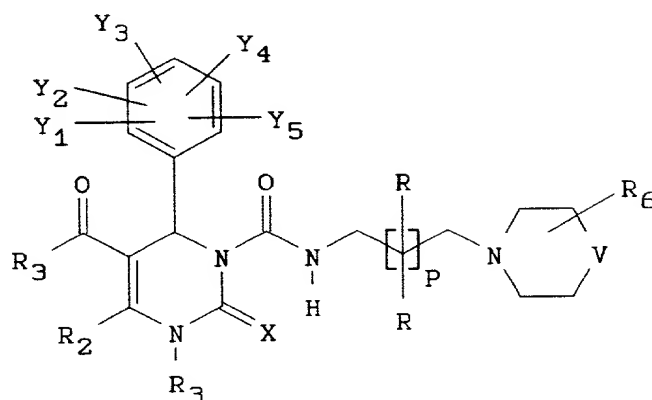
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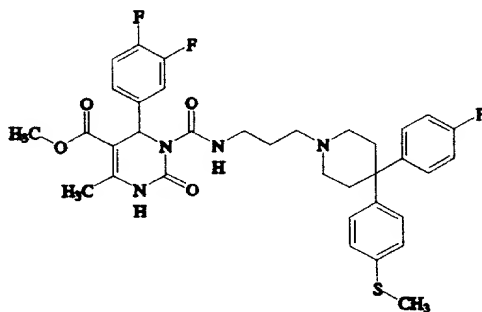
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In one embodiment of the present invention the  
5 compounds have the structure:

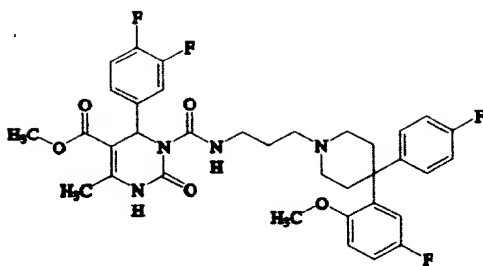


wherein V is selected from CR<sub>5</sub>R<sub>7</sub> or NR<sub>7</sub> and p is  
selected from 1-3.

In a preferred embodiment of the present invention the  
20 compounds have the following structures:

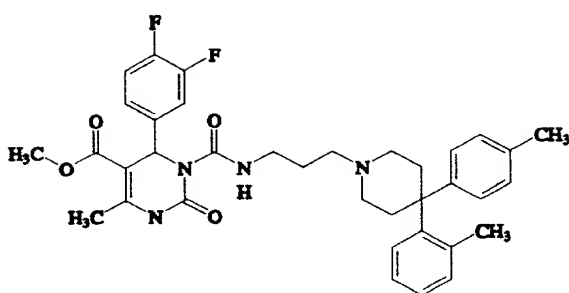


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and

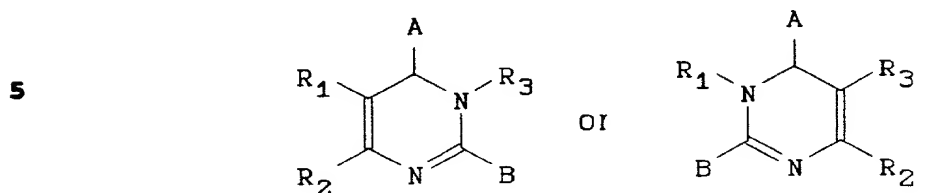
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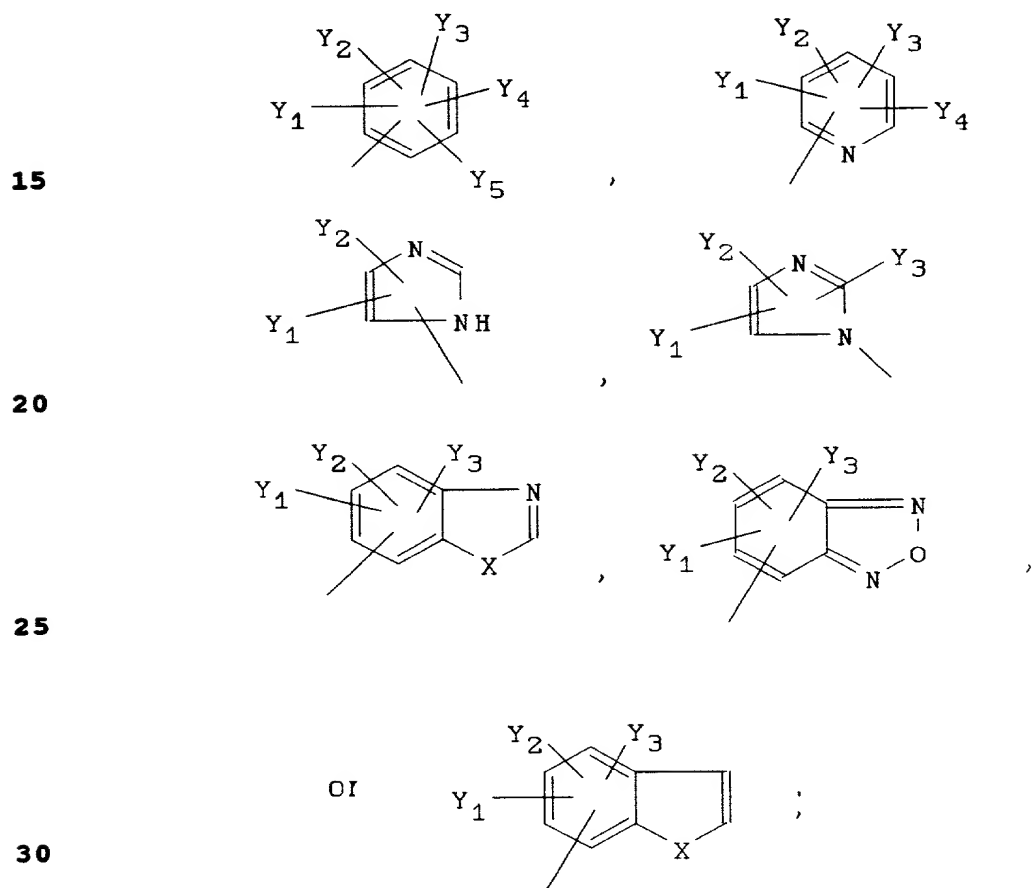
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The present invention is also directed to compounds having the structure:



10 wherein A is



35 wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ ,  $Y_4$  and  $Y_5$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl, monofluorocycloalkyl,

polyfluorocycloalkyl or cycloalkenyl; -F, -Cl, -Br, or -I; -NO<sub>2</sub>; -N<sub>3</sub>; -CN; -OR<sub>4</sub>, -OCOR<sub>4</sub>, -COR<sub>4</sub>, -CONHR<sub>4</sub>, -CON(R<sub>4</sub>)<sub>2</sub>, or -COOR<sub>4</sub>; or any two of Y<sub>1</sub>, Y<sub>2</sub>, Y<sub>3</sub>, Y<sub>4</sub> and Y<sub>5</sub> present on adjacent carbon atoms can constitute a methylenedioxy group;

wherein X is S; O; or NR<sub>4</sub>;

wherein B is -H; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl, polyfluoroalkyl, alkoxy or thioalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl; -SCH<sub>2</sub>C<sub>6</sub>H<sub>4</sub>OR<sub>4</sub>; -(CH<sub>2</sub>)<sub>n</sub>C<sub>6</sub>H<sub>5</sub>; -CH<sub>2</sub>X(CH<sub>2</sub>)<sub>p</sub>NHR<sub>4</sub>; -(CH<sub>2</sub>)<sub>n</sub>NHR<sub>4</sub>; or -OR<sub>4</sub>;

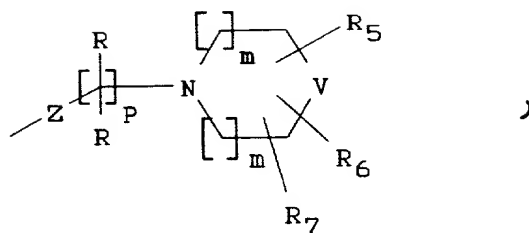
wherein R<sub>1</sub> is -H; -NO<sub>2</sub>; -CN; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; -N(R<sub>4</sub>)<sub>2</sub>; -OR<sub>4</sub>; -(CH<sub>2</sub>)<sub>p</sub>OR<sub>4</sub>; -COR<sub>4</sub>; -CO<sub>2</sub>R<sub>4</sub>; or -CON(R<sub>4</sub>)<sub>2</sub>;

wherein R<sub>2</sub> is -H; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; C<sub>3</sub>-C<sub>10</sub> cycloalkyl-C<sub>1</sub>-C<sub>10</sub>-alkyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl-C<sub>1</sub>-C<sub>10</sub>-monofluoroalkyl or C<sub>3</sub>-C<sub>10</sub> cycloalkyl-C<sub>1</sub>-C<sub>10</sub>-polyfluoroalkyl; -CN; -CH<sub>2</sub>XR<sub>4</sub>, -CH<sub>2</sub>X(CH<sub>2</sub>)<sub>p</sub>NHR<sub>4</sub>, -(CH<sub>2</sub>)<sub>n</sub>NHR<sub>4</sub>, -CH<sub>2</sub>X(CH<sub>2</sub>)<sub>p</sub>N(R<sub>4</sub>)<sub>2</sub>, -CH<sub>2</sub>X(CH<sub>2</sub>)<sub>p</sub>N<sub>3</sub>, or -CH<sub>2</sub>X(CH<sub>2</sub>)<sub>p</sub>NHCXR<sub>7</sub>; or -OR<sub>4</sub>;

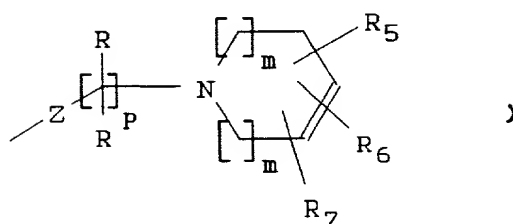
wherein each p is independently an integer from 1 to 7; wherein each n is independently an integer from 0 to 5;

wherein  $R_3$  is

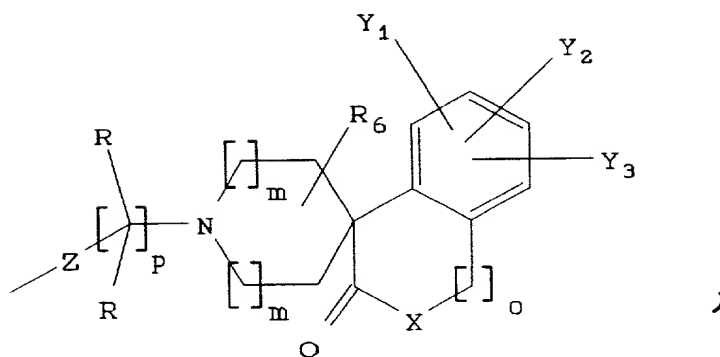
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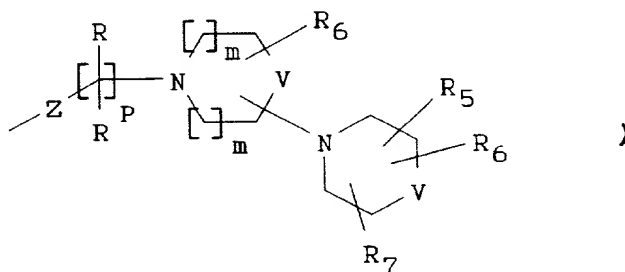


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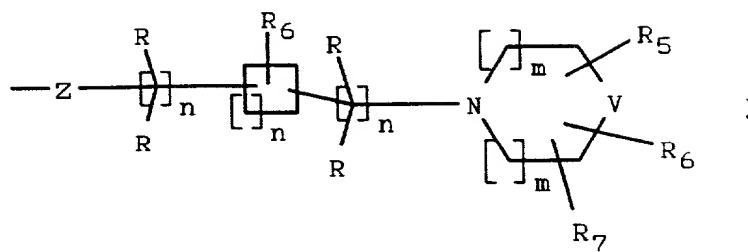
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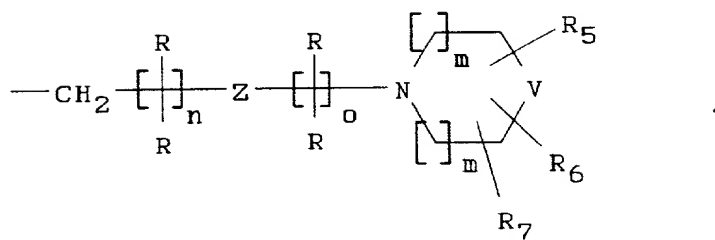
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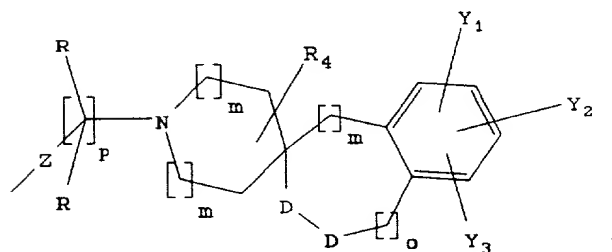


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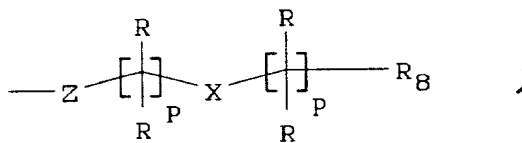
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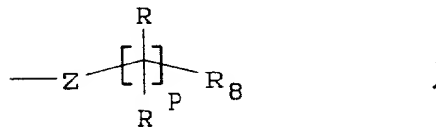


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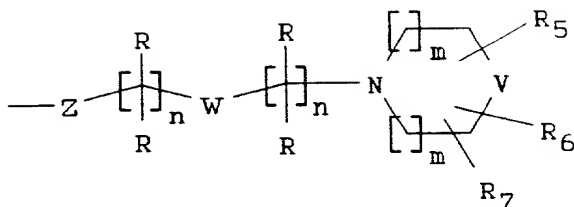
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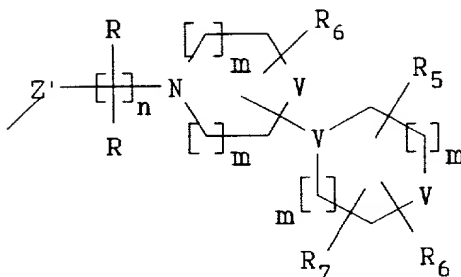
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or

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wherein Z is C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; CH<sub>2</sub>; O; CO; CO<sub>2</sub>; CONR<sub>4</sub>; S; SO; SO<sub>2</sub>; or NR<sub>4</sub>;

wherein Z' is (CH<sub>2</sub>)<sub>0</sub>, CO, (CH<sub>2</sub>)<sub>0</sub>CO, or CO(CH<sub>2</sub>)<sub>0</sub>;

25

wherein each D is independently CH<sub>2</sub>; O; S; NR<sub>4</sub>; CO; or CS;

30

wherein W is C=O; C=NOR<sub>4</sub>; substituted or unsubstituted phenyl, pyridyl, thiophenyl, furanyl, pyrazinyl, pyrrol, naphthyl, indolyl, imidazolyl, benzfurazanyl, benzfuranyl or benzyimidazolyl, wherein the phenyl, pyridyl, thiophenyl, furanyl, pyrazinyl, pyrrol, naphthyl, indolyl, imidazolyl, benzfurazanyl, benzfuranyl or benzyimidazolyl is substituted with -H, -F, -Cl, -Br, -I, -NO<sub>2</sub>, -CN, straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, straight chained or branched C<sub>1</sub>-C<sub>7</sub>

35



5 monofluoroalkyl, straight chained or branched  $C_1-C_7$  polyfluoroalkyl, straight chained or branched  $C_2-C_7$  alkenyl, straight chained or branched  $C_2-C_7$  alkynyl,  $C_3-C_7$  cycloalkyl,  $C_3-C_7$  monofluorocycloalkyl,  $C_3-C_7$  polyfluorocycloalkyl,  $C_3-C_7$  cycloalkenyl,  $-N(R_4)_2$ ,  $-OR_4$ ,  $-COR_4$ ,  $-CO_2R_4$ , or  $-CON(R_4)_2$ ;

10 wherein each V is independently O; S;  $CH_2$ ;  $CR_5R_7$ ;  $C(R_7)_2$ ; or  $NR_7$ ; provided that when V is  $CR_5R_7$  the remaining carbons on the ring may only be substituted with  $R_6$ ;

15 wherein each m is independently an integer from 0 to 3; wherein o is an integer from 1 to 3;

20 wherein each R is independently -H; -F; straight chained or branched  $C_1-C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2-C_7$  alkenyl or alkynyl;  $-N(R_4)_2$ ;  $-NO_2$ ;  $-CN$ ;  $-CO_2R_4$ ; or  $-OR_4$ ;

25 wherein each  $R_4$  is independently -H; straight chained or branched  $C_1-C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2-C_7$  alkenyl or alkynyl;  $C_3-C_7$  cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;

30 wherein  $R_5$  is aryl or heteroaryl substituted with one or more of F; Cl; Br; I;  $COR_3$ ;  $CO_2R_3$ ;  $-CON(R_3)_2$ ; CN;  $-NO_2$ ;  $-N(R_3)_2$ ;  $-OR_3$ ,  $-SR_3$ ;  $(CH_2)_oOR_3$ ;  $(CH_2)_oSR_3$ ; straight chained or branched  $C_1-C_7$  alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl, or  
35 carboxamidoalkyl; straight chained or branched  $C_2-C_7$  alkenyl,  $C_2-C_7$  alkynyl,  $C_3-C_7$  cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or

cycloalkenyl;

5 wherein each  $R_6$  is independently -H; straight  
chained or branched  $C_1-C_7$  alkyl, hydroxyalkyl,  
aminoalkyl, alkoxyalkyl, monofluoroalkyl or  
polyfluoroalkyl; straight chained or branched  $C_2-C_7$   
alkenyl or alkynyl;  $C_3-C_7$  cycloalkyl,  
monofluorocycloalkyl, polyfluorocycloalkyl or  
cycloalkenyl; or  $-OR_4$ ;

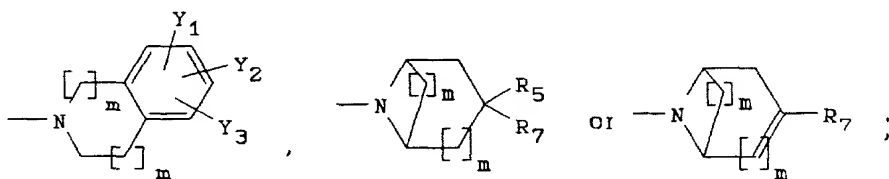
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wherein  $R_7$  is aryl or heteroaryl substituted with  
one or more of F; Cl; Br; I;  $COR_3$ ;  $CO_2R_3$ ;  $-CON(R_3)_2$ ;  
CN;  $-NO_2$ ;  $-N(R_3)_2$ ;  $-OR_3$ ,  $-SR_3$ ;  $(CH_2)_6OR_3$ ;  $(CH_2)_6SR_3$ ;  
15 straight chained or branched  $C_1-C_7$  alkyl,  
monofluoroalkyl, polyfluoroalkyl, aminoalkyl, or  
carboxamidoalkyl; straight chained or branched  
 $C_2-C_7$  alkenyl,  $C_2-C_7$  alkynyl,  $C_3-C_7$  cycloalkyl,  
monofluorocycloalkyl, polyfluorocycloalkyl or  
cycloalkenyl; and

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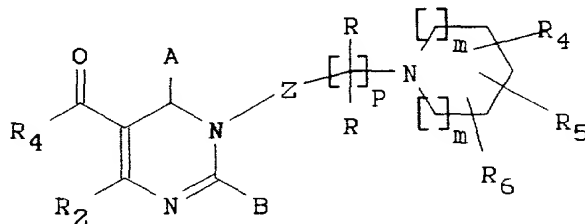
wherein  $R_8$  is -H; substituted or unsubstituted  
benzyl, benzoyl, phenyl, pyridyl, thiophenyl,  
furanyl, pyrazinyl, pyrrolyl, naphthyl, indolyl,  
imidazolyl, benzfurazanyl, benzfuranyl,  
25 benzimidazolyl or 2-keto-1-benzimidazolyl,  
wherein the benzyl, benzoyl, phenyl, pyridyl,  
thiophenyl, furanyl, pyrazinyl, pyrrolyl, naphthyl,  
indolyl, imidazolyl, benzfurazanyl, benzfuranyl,  
benzimidazolyl or 2-keto-1-benzimidazolyl is  
30 substituted with -H, -F, -Cl, -Br, -I,  $-NO_2$ , -CN,  
straight chained or branched  $C_1-C_7$  alkyl, straight  
chained or branched  $C_1-C_7$  monofluoroalkyl, straight  
chained or branched  $C_1-C_7$  polyfluoroalkyl, straight  
chained or branched  $C_2-C_7$  alkenyl, straight chained  
35 or branched  $C_2-C_7$  alkynyl,  $C_3-C_7$  cycloalkyl,  $C_3-C_7$   
monofluorocycloalkyl,  $C_3-C_7$  polyfluorocycloalkyl,  
 $C_3-C_7$  cycloalkenyl,  $-N(R_4)_2$ ,  $-OR_4$ ,  $-COR_4$ ,  $-CO_2R_4$ , or

5 -CON(R<sub>4</sub>)<sub>2</sub>; substituted or unsubstituted straight  
 chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl or  
 polyfluoroalkyl; substituted or unsubstituted  
 straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or  
 alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl or cycloalkenyl, wherein  
 the alkyl, monofluoroalkyl, polyfluoroalkyl,  
 alkenyl, alkynyl, cycloalkyl or cycloalkenyl is  
 10 substituted with -H, phenyl, pyridyl, thiophenyl,  
 furanyl, pyrazinyl, pyrrol, naphthyl, indolyl,  
 imidazolyl, benzfurazanyl, benzfuranyl,  
 benzimidazolyl, -N(R<sub>4</sub>)<sub>2</sub>, -NO<sub>2</sub>, -CN, -CO<sub>2</sub>R<sub>4</sub>, -OR<sub>4</sub>;



or a pharmaceutically acceptable salt thereof.

15 In one embodiment of the present invention the  
 compounds have the following structure:

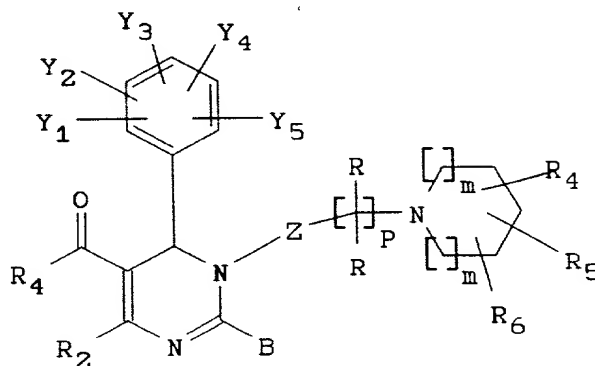


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In a further embodiment of the present invention the compounds have the structure:

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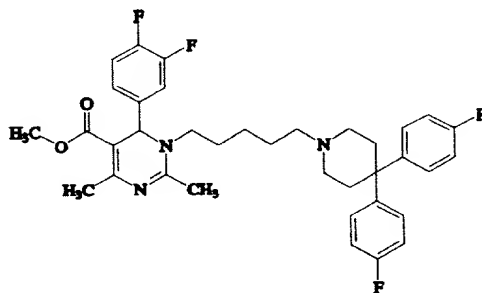
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The invention further provides for the embodiment having the following structures:

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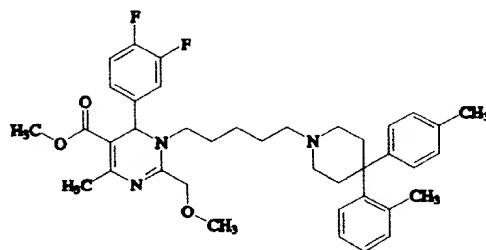
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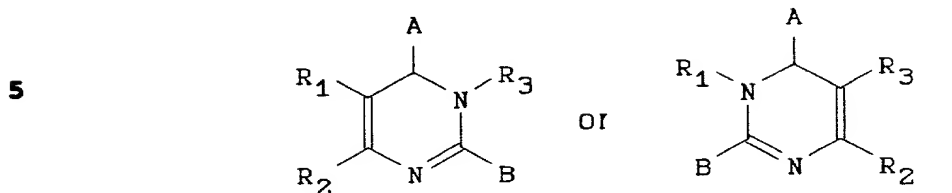
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and

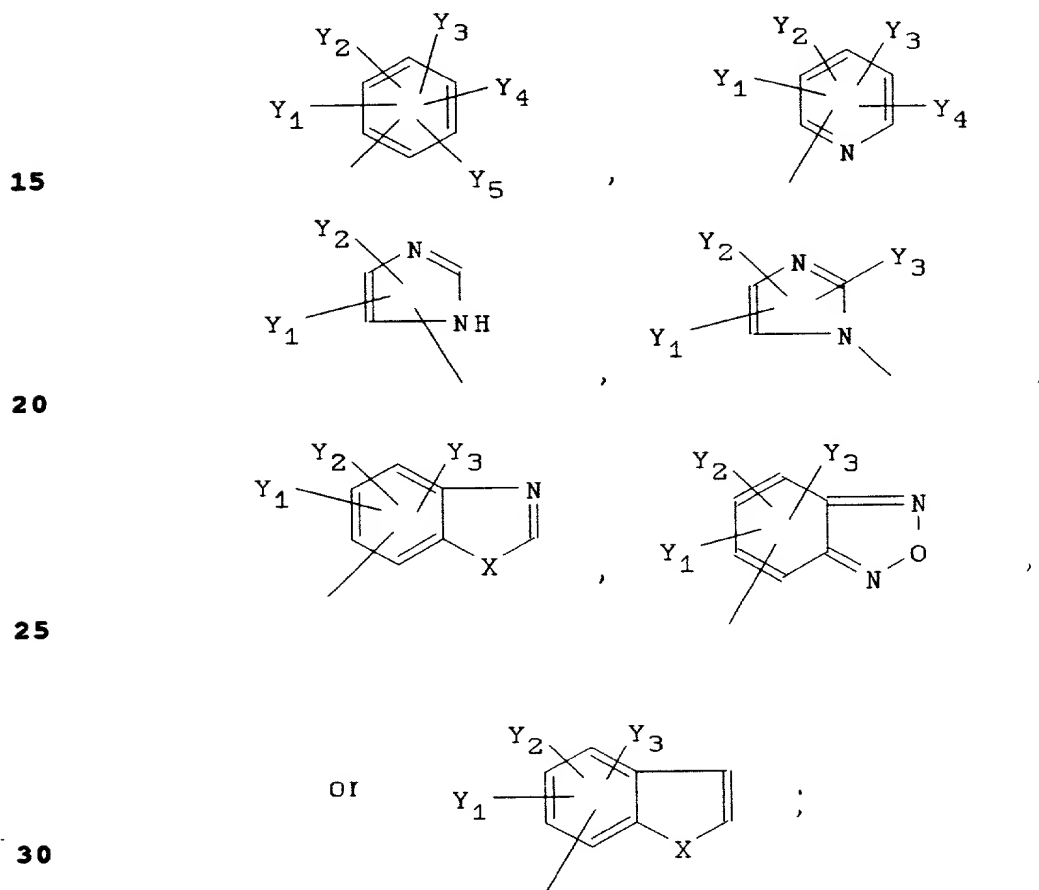
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The present invention is also directed to compounds having the structure:



10 wherein A is



35 wherein each of  $Y_1$ ,  $Y_2$ ,  $Y_3$ ,  $Y_4$  and  $Y_5$  is independently -H; straight chained or branched  $C_1$ - $C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2$ - $C_7$  alkenyl or alkynyl;  $C_3$ - $C_7$  cycloalkyl, monofluorocycloalkyl,

polyfluorocycloalkyl or cycloalkenyl; -F, -Cl, -Br, or -I; -NO<sub>2</sub>; -N<sub>3</sub>; -CN; -OR<sub>4</sub>, -OCOR<sub>4</sub>, -COR<sub>4</sub>, -CONHR<sub>4</sub>, -CON(R<sub>4</sub>)<sub>2</sub>, or -COOR<sub>4</sub>; or any two of Y<sub>1</sub>, Y<sub>2</sub>, Y<sub>3</sub>, Y<sub>4</sub> and Y<sub>5</sub> present on adjacent carbon atoms can constitute a methylenedioxy group;

wherein X is S; O; or NR<sub>4</sub>;

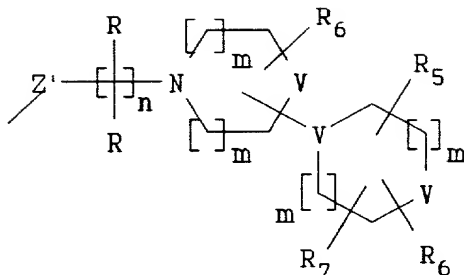
wherein B is -H; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl, polyfluoroalkyl, alkoxy or thioalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl; -SCH<sub>2</sub>C<sub>6</sub>H<sub>4</sub>OR<sub>4</sub>; -(CH<sub>2</sub>)<sub>n</sub>C<sub>6</sub>H<sub>5</sub>; -CH<sub>2</sub>X(CH<sub>2</sub>)<sub>n</sub>NHR<sub>4</sub>; -(CH<sub>2</sub>)<sub>n</sub>NHR<sub>4</sub>; or -OR<sub>4</sub>;

wherein R<sub>1</sub> is -H; -NO<sub>2</sub>; -CN; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; -N(R<sub>4</sub>)<sub>2</sub>; -OR<sub>4</sub>; -(CH<sub>2</sub>)<sub>p</sub>OR<sub>4</sub>; -COR<sub>4</sub>; -CO<sub>2</sub>R<sub>4</sub>; or -CON(R<sub>4</sub>)<sub>2</sub>;

wherein R<sub>2</sub> is -H; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; C<sub>3</sub>-C<sub>10</sub> cycloalkyl-C<sub>1</sub>-C<sub>10</sub>-alkyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl-C<sub>1</sub>-C<sub>10</sub>-monofluoroalkyl or C<sub>3</sub>-C<sub>10</sub> cycloalkyl-C<sub>1</sub>-C<sub>10</sub>-polyfluoroalkyl; -CN; -CH<sub>2</sub>XR<sub>4</sub>, -CH<sub>2</sub>X(CH<sub>2</sub>)<sub>p</sub>NHR<sub>4</sub>, -(CH<sub>2</sub>)<sub>n</sub>NHR<sub>4</sub>, -CH<sub>2</sub>X(CH<sub>2</sub>)<sub>p</sub>N(R<sub>4</sub>)<sub>2</sub>, -CH<sub>2</sub>X(CH<sub>2</sub>)<sub>p</sub>N<sub>3</sub>, or -CH<sub>2</sub>X(CH<sub>2</sub>)<sub>p</sub>NHCXR<sub>7</sub>; or -OR<sub>4</sub>;

wherein each p is independently an integer from 1 to 7; wherein each n is independently an integer from 0 to 5;

wherein  $R_3$  is



wherein  $Z'$  is  $(CH_2)_o$ ,  $CO$ ,  $(CH_2)_oCO$ , or  $CO(CH_2)_o$ ;

wherein each  $V$  is independently  $O$ ;  $S$ ;  $CH_2$ ;  $CR_5R_7$ ;  $C(R_7)_2$ ; or  $NR_7$ ;

wherein each  $m$  is independently an integer from 0 to 3; wherein  $o$  is an integer from 1 to 3;

wherein each  $R$  is independently  $-H$ ;  $-F$ ; straight chained or branched  $C_1-C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2-C_7$  alkenyl or alkynyl;  $-N(R_4)_2$ ;  $-NO_2$ ;  $-CN$ ;  $-CO_2R_4$ ; or  $-OR_4$ ;

wherein each  $R_4$  is independently  $-H$ ; straight chained or branched  $C_1-C_7$  alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched  $C_2-C_7$  alkenyl or alkynyl;  $C_3-C_7$  cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;

wherein  $R_5$  and  $R_7$  each independently may be  $-H$ ;  $F$ ;  $Cl$ ;  $Br$ ;  $I$ ;  $-COR_3$ ;  $-CO_2R_3$ ;  $-CON(R_3)_2$ ;  $-CN$ ;  $-NO_2$ ;  $-N(R_3)_2$ ;  $-OR_3$ ;  $-SR_3$ ;  $-(CH_2)_pOR_3$ ;  $-(CH_2)_pSR_3$ ; straight chained or branched  $C_1-C_7$  alkyl, aminoalkyl, carboxamidoalkyl; straight chained or branched

C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl, or C<sub>3</sub>-C<sub>7</sub> cycloalkyl or cycloalkenyl; wherein the alkyl, aminoalkyl, carboxamidoalkyl, alkenyl, alkynyl, cycloalkyl or cycloalkenyl may be substituted with one or more aryl or heteroaryl, wherein the aryl or heteroaryl may be substituted with -F, -Cl, -Br, -I, -NO<sub>2</sub>, -CN, -OR<sub>3</sub>, -SR<sub>3</sub>, C<sub>1</sub>-C<sub>3</sub> alkyl, or carboxamido; aryl or heteroaryl, wherein the aryl or heteroaryl may be substituted with one or more -F, -Cl, -Br, -I, COR<sub>3</sub>, CO<sub>2</sub>R<sub>3</sub>, -CON(R<sub>3</sub>)<sub>2</sub>, -CN, -NO<sub>2</sub>, -N(R<sub>3</sub>)<sub>2</sub>, -OR<sub>3</sub>, -SR<sub>3</sub>, (CH<sub>2</sub>)<sub>6</sub>OR<sub>3</sub>, (CH<sub>2</sub>)<sub>6</sub>SR<sub>3</sub>; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl, C<sub>2</sub>-C<sub>7</sub> alkynyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; and

wherein each R<sub>6</sub> is independently -H; straight chained or branched C<sub>1</sub>-C<sub>7</sub> alkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C<sub>2</sub>-C<sub>7</sub> alkenyl or alkynyl; C<sub>3</sub>-C<sub>7</sub> cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; or -OR<sub>4</sub>;

or a pharmaceutically acceptable salt thereof.

In the present invention aryl includes phenyl, benzyl, benzoyl or naphthyl and heteroaryl includes pyrazinyl, pyrrolyl, furanyl, thiophenyl, pyridyl, imidazolyl, indolyl, aminophenyl, benzamidyl, benzimidazolyl, benzfurazanyl, benzfuranyl, 2-keto-1-benzimidazolyl or quinolyl.

The invention further provides for a pharmaceutical composition comprising a therapeutically effective amount of any of the compounds described above and a



pharmaceutically acceptable carrier. In the subject invention a "therapeutically effective amount" is any amount of a compound which, when administered to a subject suffering from a disease against which the compounds are effective, causes reduction, remission, or regression of the disease. In one embodiment the therapeutically effective amount is an amount from about 0.01 mg per subject per day to about 500 mg per subject per day, preferably from about 0.1 mg per subject per day to about 60 mg per subject per day and most preferably from about 1 mg per subject per day to about 20 mg per subject per day. In the practice of this invention the "pharmaceutically acceptable carrier" is any physiological carrier known to those of ordinary skill in the art useful in formulating pharmaceutical compositions.

In one preferred embodiment the pharmaceutical carrier may be a liquid and the pharmaceutical composition would be in the form of a solution. In another equally preferred embodiment, the pharmaceutically acceptable carrier is a solid and the composition is in the form of a powder or tablet. In a further embodiment, the pharmaceutical carrier is a gel and the composition is in the form of a suppository or cream.

The invention provides a method of treating a subject suffering from benign prostatic hyperplasia which comprises administering to the subject any one of the compounds described herein effective to treat benign prostatic hyperplasia. In a preferred embodiment the compound of the pharmaceutical composition additionally does not cause a fall in blood pressure at dosages effective to alleviate benign prostatic hyperplasia. In one preferred embodiment the compound effects treatment of benign prostatic hyperplasia by relaxing lower urinary tract tissue and in particular where

lower urinary tract tissue is prostatic smooth muscle.

5 The invention further provides a method of treating a subject suffering from elevated intraocular pressure which comprises administering to the subject one of the compounds described herein effective to lower intraocular pressure.

10 The invention further provides a method of treating a subject suffering from a disorder associated with elevated blood cholesterol which comprises administering to the subject one of the compounds described herein effective to inhibit cholesterol synthesis.

15 The invention also provides a method of treating a disease which is susceptible to treatment by antagonism of the  $\alpha_{1A}$  receptor which comprises administering to the subject one of the compounds described herein effective to treat the disease.

20 The invention further provides a method of treating a subject suffering from impotency which comprises administering to the subject one of the compounds described herein effective to treat impotency.

25 The invention further provides a method of treating a subject suffering from sympathetically mediated pain which comprises administering to the subject one of the compounds described herein effective to treat sympathetically mediated pain.

30 The invention provides a method of treating a subject suffering from cardiac arrhythmia which comprises administering to the subject one of the compounds described herein effective to treat cardiac arrhythmia.

35

The invention provides a method of treating a subject suffering from benign prostatic hyperplasia which comprises administering to the subject one of the compounds described herein in combination with a 5  
5 alpha-reductase inhibitor effective to treat benign prostatic hyperplasia. In one preferred embodiment the 5-alpha reductase inhibitor is finasteride. The dosage administered to the subject is about 0.01 mg per subject per day to 50 mg per subject per day of  
10 finasteride in combination with an  $\alpha_{1A}$  antagonist. A more preferred dosage administered to the subject is about 1 mg per subject per day to 7 mg per subject per day of finasteride in combination with an  $\alpha_{1A}$  antagonist. The most preferred dosage administered to  
15 the subject is about 5 mg per subject per day of finasteride in combination with an  $\alpha_{1A}$  antagonist.

The invention also provides for a pharmaceutical composition comprising a therapeutically effective  
20 amount of a combination of any of the compounds described herein in combination with finasteride and a pharmaceutically acceptable carrier. In one embodiment the pharmaceutical composition is a therapeutically effective amount of a combination comprising an amount  
25 from about 0.01 mg per subject per day to about 500 mg per subject per day of any one of the compounds described herein and an amount of finasteride of about 5 mg per subject per day. A more preferred embodiment of the pharmaceutical composition is a therapeutically  
30 effective amount of a combination comprising an amount from about 0.1 mg per subject per day to about 60 mg per subject per day of any one of the compounds described herein and an amount of the finasteride of about 5 mg per subject per day. The most preferred  
35 embodiment of the pharmaceutical composition is a therapeutically effective amount of a combination comprising from about 1 mg per subject per day to about

20 mg per subject per day of any one of the compounds described herein and an amount of finasteride of about 5 mg per subject per day.

5 The invention further provides a method of relaxing lower urinary tract tissue which comprises contacting the lower urinary tract tissue with an amount of one of the compounds described herein effective to relax lower urinary tract tissue. In one embodiment the lower urinary tract tissue is prostatic smooth muscle. In one preferred embodiment the compound additionally does not cause a fall in blood pressure when it is effective to relax lower urinary tract tissue.

10 The invention provides a method of relaxing lower urinary tract tissue in a subject which comprises administering to the subject an amount of one of the compounds described herein effective to relax lower urinary tract tissue. In one preferred embodiment the compound does not cause a fall in blood pressure and the lower urinary tract tissue is prostatic smooth muscle.

15 The invention further provides for a method of inhibiting contraction of prostatic tissue, which comprises administering to the subject an amount of any of the compounds described herein effective to inhibit contraction of prostatic tissue. In one preferred embodiment the prostatic tissue is prostatic smooth muscle and the compound additionally does not cause a fall in blood pressure.

20 The invention provides for the use of the compounds described herein for the preparation of a pharmaceutical composition for lowering intraocular pressure, inhibiting cholesterol synthesis, and the treatment of: benign prostatic hyperplasia, impotency,

cardiac arrhythmia and any disease where antagonism of the  $\alpha_{1A}$  receptor may be useful. The invention provides for the use of the compounds described herein for the preparation of a pharmaceutical composition for relaxing lower urinary tract tissue and in particular prostatic smooth muscle. The invention further provides for the use of any of compounds described herein for the preparation of a pharmaceutical composition, where the compound additionally does not cause a fall in blood pressure at dosages effective to lower intraocular pressure, to inhibit cholesterol synthesis, and for the treatment of: benign prostatic hyperplasia, impotency, cardiac arrhythmia and any disease where antagonism of the  $\alpha_{1A}$  receptor may be useful.

The invention provides for the use of the compounds described herein in the preparation of a medicament for lowering intraocular pressure, inhibiting cholesterol synthesis, and for the treatment of: benign prostatic hyperplasia, impotency, cardiac arrhythmia and any disease where antagonism of the  $\alpha_{1A}$  receptor may be useful. The invention provides for the use of the compounds described herein in the preparation of a medicament for relaxing lower urinary tract tissue and in particular prostatic smooth muscle. The invention further provides for the use of any of compounds described herein in the preparation of a medicament, where the compound additionally does not cause a fall in blood pressure at dosages effective to lower intraocular pressure, to inhibit cholesterol synthesis, and for the treatment of: benign prostatic hyperplasia, impotency, cardiac arrhythmia and any disease where antagonism of the  $\alpha_{1A}$  receptor may be useful.

The invention provides for a drug which is useful for lowering intraocular pressure, inhibiting cholesterol

synthesis, and the treatment of: benign prostatic hyperplasia, impotency, cardiac arrhythmia and any disease where antagonism of the  $\alpha_{1A}$  receptor may be useful, the effective ingredient of the said drug being any of the compounds described herein. The invention further provides the drug described herein additionally does not cause a fall in blood pressure at dosages effective to lower intraocular pressure, to inhibit cholesterol synthesis, and for the treatment of: benign prostatic hyperplasia, impotency, cardiac arrhythmia and any disease where antagonism of the  $\alpha_{1A}$  receptor may be useful.

The invention provides for a drug which is useful for relaxing lower urinary tract tissue and in particular prostatic smooth muscle, the effective ingredient of the drug being any of the compounds described herein. The invention further provides the drug which is useful for relaxing lower urinary tract tissue additionally does not cause a fall in blood pressure at dosages effective to relax lower urinary tract tissue.

The invention also provides for the (-) and (+) enantiomers of all compounds of the subject application described herein. Included in this invention are pharmaceutically acceptable salts and complexes of all of the compounds described herein. The salts include but are not limited to the following acids and bases. The following inorganic acids; hydrochloric acid, hydrofluoric acid, hydrobromic acid, hydroiodic acid, sulfuric acid and boric acid. The organic acids; acetic acid, trifluoroacetic acid, formic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, maleic acid, citric acid, methanesulfonic acid, trifluoromethanesulfonic acid, benzoic acid, glycolic acid, lactic acid and mandelic acid. The following inorganic bases; ammonia,

hydroxyethylamine and hydrazine. The following organic bases; methylamine, ethylamine, propylamine, dimethylamine, diethylamine, trimethylamine, triethylamine, ethylenediamine, hydroxyethylamine, morpholine, piperazine and guanidine. This invention further provides for the hydrates and polymorphs of all of the compounds described herein.

In one preferred embodiment the pharmaceutical carrier may be a liquid and the pharmaceutical composition would be in the form of a solution. In another equally preferred embodiment, the pharmaceutically acceptable carrier is a solid and the composition is in the form of a powder or tablet. In a further embodiment, the pharmaceutical carrier is a gel and the composition is in the form of a suppository or cream. In a further embodiment the compound may be formulated as a part of a pharmaceutically acceptable transdermal patch.

A solid carrier can include one or more substances which may also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents; it can also be an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, polyvinylpyrrolidone, low melting waxes and ion exchange resins.

Liquid carriers are used in preparing solutions,

suspensions, emulsions, syrups, elixirs and pressurized compositions. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fats. The liquid carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmoregulators. Suitable examples of liquid carriers for oral and parenteral administration include water (partially containing additives as above, e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g. glycols) and their derivatives, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration, the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are useful in sterile liquid form compositions for parenteral administration. The liquid carrier for pressurized compositions can be halogenated hydrocarbon or other pharmaceutically acceptable propellant.

Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by for example, intramuscular, intrathecal, epidural, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. The compounds may be prepared as a sterile solid composition which may be dissolved or suspended at the time of administration using sterile water, saline, or other appropriate sterile injectable medium. Carriers are intended to include necessary and inert binders, suspending agents, lubricants, flavorants, sweeteners, preservatives, dyes, and coatings.



5 The compound can be administered orally in the form of a sterile solution or suspension containing other solutes or suspending agents, for example, enough saline or glucose to make the solution isotonic, bile salts, acacia, gelatin, sorbitan monoleate, polysorbate 80 (oleate esters of sorbitol and its anhydrides copolymerized with ethylene oxide) and the like.

10 The compound can also be administered orally either in liquid or solid composition form. Compositions suitable for oral administration include solid forms, such as pills, capsules, granules, tablets, and powders, and liquid forms, such as solutions, syrups, elixirs, and suspensions. Forms useful for parenteral  
15 administration include sterile solutions, emulsions, and suspensions.

20 Optimal dosages to be administered may be determined by those skilled in the art, and will vary with the particular compound in use, the strength of the preparation, the mode of administration, and the advancement of the disease condition. Additional factors depending on the particular subject being treated will result in a need to adjust dosages,  
25 including subject age, weight, gender, diet, and time of administration.

30 One skilled in the art will readily appreciate that appropriate biological assays will be used to determine the therapeutic potential of the claimed compounds for the treating the above noted disorders.

35 This invention will be better understood from the Experimental Details which follow. However, one skilled in the art will readily appreciate that the specific methods and results discussed are merely illustrative of the invention as described more fully

in the claims which follow thereafter.

[illegible]

## Experimental Details

For Examples 1-92 Scheme 1 describes the general synthetic preparation. All NMRs were obtained using a 300MHz GE QEPLUS NMR machine.

### Example 1

**1,6-Dihydro-5-methoxycarbonyl-2-[(4-methoxyphenyl)methyl]thio]-4-methyl-6-(4-nitrophenyl)-1-[N-[3-(4,4-diphenylpiperidin-1-yl)propyl]}carboxamido pyrimidine.**

a. **4,4-Diphenylpiperidine hydrochloride.** A mixture of 4-piperidone monohydrate hydrochloride (15.0 g, 0.0976 mol) and  $\text{AlCl}_3$  (130 g, 0.976 mol, 10.0 eq) in anhydrous benzene (600 mL) were stirred at reflux for 4 hours. The mixture was cooled to room temperature, poured into ice (300 g) and water (50 mL), and filtered. The solid was washed with toluene and dried to afford 19.2 g (72%) of an off-white solid, which was characterized spectroscopically.

b. **3-(4,4-Diphenylpiperidin-1-yl)propionitrile.** To a suspension of 4,4-diphenylpiperidine hydrochloride (0.195 g, 0.712 mmol) in EtOH (1.5 mL) was added  $\text{Et}_3\text{N}$  (0.25 mL, 1.8 mmol, 2.6 eq) followed by acrylonitrile (0.13 mL, 2.01 mmol, 2.8 eq). The resulting solution was stirred at room temperature under argon for 15 min and then concentrated. Water was added, and the mixture was extracted with EtOAc (3 X 10 mL). The combined organic extracts were dried ( $\text{MgSO}_4$ ) and concentrated to give 170 mg (87%) of a tan solid, which was characterized spectroscopically and used in the next reaction without purification.

c. **3-(4,4-Diphenylpiperidin-1-yl)propylamine.** To a stirred solution of 3-(4,4-diphenylpiperidin-1-

yl)propionitrile (2.00 g, 6.89 mmol) in anhydrous THF (20 mL) under argon was added a solution of  $\text{BH}_3$  in THF (1.0 M, 24.1 mL, 24 mmol, 3.5 eq) at room temperature. The mixture was refluxed for 4.5 hours and then cooled to room temperature. Aqueous HCl (6 N, 50 mL) was added and stirring was continued for 1 hour. The mixture was basified to pH 9 by addition of 6 N aq. NaOH, extracted with  $\text{CH}_2\text{Cl}_2$  (3 X 10 mL), dried ( $\text{MgSO}_4$ ) and concentrated. The residue was purified by flash chromatography ( $\text{SiO}_2$ , EtOAc-MeOH-isopropylamine 9:1:0 to 4:1:0.2) to give 1.35 g (66%) of tan solid, which was characterized spectroscopically.

**d. 2-(4-Methoxybenzyl)-2-thiopseudourea hydrochloride.**

To a well-stirred suspension of thiourea (7.6 g, 0.1 mol) in THF (50 mL) at 0 °C, 4-methoxybenzyl chloride (16 g, 0.1 mol) was added in 10 min and the mixture was allowed to warm to room temperature. After 2 hours the mixture was heated to 65 °C and kept at that temperature for 5 hours. It was cooled to room temperature and diluted with diethyl ether (200 mL). The white precipitate formed was filtered and dried (22.5 g, 96%); m. p. 161-163 °C.

**e. Methyl 2-[(4-nitrophenyl)methylene]-3-oxobutyrates.** A mixture of 4-nitrobenzaldehyde (15.1 g, 0.1 mol), methyl acetoacetate (12.773 g, 0.11 mol), piperidine (0.41 g, 476 mL, 4.8 mmol), and acetic acid (0.288 g, 274 mL, 4.8 mmol) in 2-propanol (400 mL) was stirred at room temperature for 48 hours. The white solid, methyl 2-[(4-nitrophenyl)methylene]-3-oxobutyrates, formed was filtered, washed with 2-propanol (2 X 50 mL) and dried (21.80 g, 93%).

**f. 1,6-Dihydro-5-methoxycarbonyl-2-[(4-methoxyphenyl)methyl]thio]-4-methyl-6-(4-nitrophenyl)pyrimidine.** A

mixture of methyl 2-[(4-nitrophenyl)methylene]-3-oxobutyr-  
ate (8.96 g, 0.04 mol), 2-(4-methoxybenzyl)-2-thiopseudourea hydrochloride (9.28 g, 0.04 mol), and NaOAc (3.28 g, 0.04 mol) in DMF (100 mL) was stirred  
5 and heated at 70-75 °C for 4.5 hours. The mixture was cooled, poured into ice-water (300 mL), extracted with EtOAc (2 X 400 mL). The combined EtOAc extracts were washed with 10% NaHCO<sub>3</sub> solution (2 X 60 mL), brine (100 mL), and dried (MgSO<sub>4</sub>). Solvent was evaporated and the  
10 crude product was purified by flash column chromatography on silica gel using 10% through 30% EtOAc in hexane as the gradient eluent, to leave the product as an oil, which on trituration with EtOAc/hexane became a yellow solid (11.4 g, 66.7%);  
15 m.p. 138-139 °C; <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 2.15 (s, 3 H), 3.62 (s, 3 H), 3.72 (s, 3 H), 4.05, 5.78 (s, d, J = 3 Hz, 1 H), 4.08, 4.20 (AB q, J = 12.5 Hz, 2 H), 4.21, 6.40 (s, d, J = 3 Hz, 1 H), 6.66 (2 d, J = 8.5 Hz, 2 H), 7.08 (2 d, J = 8.5 Hz, 2 H), 7.37 (2 d, J = 8.8 Hz, 2 H), 8.7  
20 (2 d, J = 8.8 Hz, 2 H); Anal. Calcd. for C<sub>21</sub>H<sub>21</sub>N<sub>3</sub>O<sub>5</sub>S: C, 59.00; H, 4.95; N, 9.83. Found: C, 59.02; H, 4.93; N, 9.77.

**g. 1,6-Dihydro-5-methoxycarbonyl-2-[(4-methoxyphenyl)methyl]thio]-4-methyl-6-(4-nitrophenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine.**

To a well-stirred mixture of 1,6-dihydro-5-methoxycarbonyl-2-[(4-methoxyphenyl)methyl]thio]-4-methyl-6-(4-nitrophenyl)pyrimidine (4.5 g, 0.0105 mol), NaHCO<sub>3</sub>  
30 (3.69 g, 0.044 mol), CH<sub>2</sub>Cl<sub>2</sub> (200 mL), and water (50 mL) at 0-5 °C, 4-nitrophenyl chloroformate (2.4 g, 0.0119 mol) was added in 5 min and the mixture was allowed to warm to room temperature. After 10 hours, the TLC analysis of the reaction mixture showed the presence of  
35 a small amount of starting pyrimidine, therefore, more 4-nitrophenyl chloroformate (0.65 g, 0.0032 mol) was added and the stirring continued for an additional 4

hours. The two layers were separated, the  $\text{CH}_2\text{Cl}_2$  layer was washed with saturated aqueous  $\text{NaHCO}_3$  solution (3 X 50 mL), dried ( $\text{MgSO}_4$ ), and the solvent evaporated. The residue was recrystallized from  $\text{CH}_2\text{Cl}_2$  and hexane to give the product as white crystals (5.5 g, 88.4%); m.p. 156-157 °C;  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  2.53 (s, 3 H), 3.70 (s, 3 H), 3.81 (s, 3 H), 4.06, 4.36 (AB q,  $J$  = 13.5 Hz, 2 H), 6.30 (s, 1 H), 6.78 (d,  $J$  = 8.7 Hz, 2 H), 7.17 (d,  $J$  = 8.5 Hz, 2 H), 7.20 (d,  $J$  = 8.7 Hz, 2 H), 7.32 (d,  $J$  = 8.8 Hz, 2 H), 7.97 (d,  $J$  = 8.8 Hz, 2 H), 8.25 (d,  $J$  = 8.8 Hz, 2 H); Anal. Calcd. for  $\text{C}_{28}\text{H}_{24}\text{N}_4\text{O}_9\text{S}$ : C, 56.75; H, 4.08; N, 9.45. Found: C, 56.49; H, 4.28; N, 9.25.

**h. 1,6-Dihydro-5-methoxycarbonyl-2-[(4-methoxyphenyl)methyl]thio]-4-methyl-6-(4-nitrophenyl)-1-[N-[3-(4,4-diphenylpiperidin-1-yl)prop-yl]carboxamido]pyrimidine.**

To a stirred solution of 1,6-dihydro-5-methoxycarbonyl-2-[(4-methoxyphenyl)methyl]thio]-4-methyl-6-(4-nitrophenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine (0.592 g, 1 mmol) in anhydrous THF (10 mL) at room temperature under argon atmosphere, a solution of 3-[4,4-diphenylpiperidin-1-yl]propylamine (0.441 g, 1.5 mmol, 1.5 eq) in THF (5 mL) was added and the stirring continued for 1 hours. Solvent was evaporated from the reaction mixture and the residue was redissolved in  $\text{CH}_2\text{Cl}_2$  (50 mL), washed with 5%  $\text{NaHCO}_3$  (3 X 25 mL), brine (50 mL), and dried ( $\text{MgSO}_4$ ). Solvent was evaporated and the residue was purified by flash chromatography on silica gel using 10% methanol in EtOAc as the eluent to give the desired product as an oil, which on trituration with hexane and drops of EtOAc became a white powder (0.32 g, 43%); m.p. 79-80 °C;  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  1.61-1.82 (m, 4 H), 2.27 (s, 3 H), 2.30-2.51 (m, 8 H), 3.19-3.36 (m, 1 H), 3.42-3.60 (m, 1 H), 3.68 (s, 3 H), 3.76 (s, 3 H), 3.95, 4.22 (AB q,  $J$  = 13.6 Hz, 2 H), 6.16 (s, 1 H), 6.70 (d,  $J$  = 8.6 Hz, 2 H), 7.04

(d,  $J = 8.6$  Hz, 2 H), 7.11-7.29 (m, 12 H), 7.68 (br t, 1 H, NH), 7.91 (d,  $J = 8.8$  Hz, 2 H); Anal. Calcd. for  $C_{42}H_{45}N_5O_6S \cdot 0.33 CH_2Cl_2$ : C, 65.52; H, 5.93; N, 9.03. Found: C, 65.52; H, 6.01; N, 9.20.

5

### Example 2

**1,6-Dihydro-5-methoxycarbonyl-2-[(4-methoxyphenyl)methyl]thio]-4-methyl-6-(4-nitrophenyl)-1-[N-[3-(4-phenylpiperidin-1-yl)propyl]carboxamidopyrimidine.**

10

**a. 3-(4-Phenylpiperidin-1-yl)propionitrile.** Acrylonitrile (3.1 mL, 44 mmol, 2.5 eq) was added to a solution of 4-phenylpiperidine (3.0 g, 18 mmol) in EtOH (40 mL) and the mixture was stirred at room temperature for 1.5 hours. The volatiles were removed to give 3.8 g of pure product (brown oil, 99%), which was characterized spectroscopically.

15

**b. 3-(4-Phenylpiperidin-1-yl)propylamine.** To a stirred solution of 3-(4-phenylpiperidin-1-yl)propionitrile (5.1 g, 24 mmol) in anhydrous THF (20 mL) under argon was added a solution of  $BH_3$  in THF (1.0 M, 83 mL, 83 mmol, 3.5 eq) at room temperature. The mixture was refluxed for 4.5 hours and then cooled to room temperature. Aqueous HCl (6 N, 130 mL) was added and stirring was continued for 2 hours at 50-70 °C. The mixture was basified to pH 9 by addition of 6 N aq. NaOH and extracted with EtOAc (100 mL) and  $CH_2Cl_2$  (3 x 100 mL). The combined organic extracts were dried ( $MgSO_4$ ) and concentrated. The residue was dissolved in  $CH_2Cl_2$  (20 mL) and treated with HCl in ether (1.0 M, 50 mL). The solvents were removed, ether (250 mL) was added, the mixture was filtered, and the filter cake was washed with ether. Water (60 mL) was added to the resulting white solid, the pH was adjusted to 10-11 with 1 N NaOH, and the aqueous phase was extracted with  $CH_2Cl_2$  (3 X 50 mL). The combined extracts were dried

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(MgSO<sub>4</sub>) and the solvents evaporated to give 4.5 g (87%) of pure product (light brown solid), which was characterized spectroscopically.

5      c. 1,6-Dihydro-5-methoxycarbonyl-2- [{(4-methoxyphenyl)  
methyl}thio]-4-methyl-6-(4-nitrophenyl)-1-{N-[3-  
10      (4-phenylpiperidin-1-yl)propyl]}carboxamido  
pyrimidine. This compound was prepared from  
1,6-dihydro-5-methoxycarbonyl-2- [{(4-methoxyphenyl)  
10      methyl}thio]-4-methyl-6-(4-nitrophenyl)-1-[(4-nitroph  
enyloxy)carbonyl]pyrimidine (0.77 g, 1.3 mmol), 3-[4-  
phenylpiperidin-1-yl] propylamine (0.34 g, 1.56 mmol,  
1.2 eq) and purified using similar conditions described  
in Example 1 (0.63 g, 72%); m.p. 123-124 °C; <sup>1</sup>H-NMR  
15      (CDCl<sub>3</sub>): δ 1.65-2.10 (m, 8 H), 2.41 (s, 3 H), 2.41-2.55  
(m, 3 H), 2.99-3.06 (m, 2 H), 3.2-3.35 (m, 1 H), 3.45-  
3.60 (m, 1 H), 3.67 (s, 3 H), 3.75 (s, 3 H), 4.10, 4.33  
(AB q, J = 13.6 Hz, 2 H), 6.19 (s, 1 H), 6.71 (d, J =  
8.6 Hz, 2 H), 7.09 (d, J = 8.6 Hz, 2 H), 7.20-7.34 (m,  
20      7 H), 7.97 (br t, 1 H, NH), 7.97 (d, J = 8.8 Hz, 2 H);  
Anal. Calcd. for C<sub>36</sub>H<sub>41</sub>N<sub>5</sub>O<sub>6</sub>S.0.25 CH<sub>2</sub>Cl<sub>2</sub>: C, 62.82; H,  
6.04; N, 10.11. Found: C, 62.54; H, 6.13; N, 10.03.

### Example 3

25      1-{N-[3-(4-Cyano-4-phenylpiperidin-1-yl)propyl]}  
carboxamido-1,6-dihydro-5-methoxycarbonyl-2- [{(4-meth  
oxyphenyl)methyl}thio]-4-methyl-6-(4-nitrophenyl)  
pyrimidine.

30      a. 3-(4-Cyano-4-phenylpiperidinyl)propylamine. 4-  
Cyano-4-phenylpiperidine hydrochloride (5.01 g, 22.5  
mmol) was added to water (100 mL), and the solution was  
basified to pH 10-11 by addition of 6 N aqueous NaOH.  
The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 100 mL). The  
35      combined organic extracts were dried (MgSO<sub>4</sub>) and  
concentrated. To the residue were added 3-  
bromopropylamine hydrobromide (4.92 g, 22.5 mmol),



anhydrous  $K_2CO_3$  (3.42 g, 24.8 mmol, 1.10 eq), and 1,4-dioxane (100 mL). The mixture was stirred at reflux for 24 hours under a  $CaSO_4$  drying tube. The solvent was evaporated, and the product was purified by flash chromatography ( $SiO_2$ ,  $CHCl_3/MeOH/2$  M  $NH_3$  in MeOH (100:8:4 to 100:20:8) to give 3.23 g (59%) of colorless oil, which was characterized spectroscopically.

**b. 1-{N-[3-(4-Cyano-4-phenylpiperidin-1-yl)propyl]}carboxamido-1,6-dihydro-5-methoxycarbonyl-2-[(4-methoxy-phenyl)methyl]thio]-4-methyl-6-(4-nitrophenyl)pyrimidine.**

This compound was prepared from 1,6-dihydro-5-methoxycarbonyl-2-[(4-methoxyphenyl)methyl]thio]-4-methyl-6-(4-nitrophenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine (0.592 g, 1 mmol), 3-[4-cyano-4-phenylpiperidin-1-yl]propylamine (0.292 g, 1.2 mmol, 1.2 eq) and purified using similar conditions described in Example 1 (0.445 g, 64%); m.p. 143-144 °C;  $^1H$ -NMR ( $CDCl_3$ ):  $\delta$  1.70-1.86 (m, 2 H), 2.02-2.09 (m, 4 H), 2.38 (s, 3 H), 2.41-2.56 (m, 4 H), 2.95-3.02 (m, 2 H), 3.24-3.40 (m, 1 H), 3.42-3.58 (m, 1 H), 3.68 (s, 3 H), 3.76 (s, 3 H), 4.08, 4.23 (AB q,  $J$  = 13.5 Hz, 2 H), 6.23 (s, 1 H), 6.72 (d,  $J$  = 8.6 Hz, 2 H), 6.94 (br t, 1 H, NH), 7.08 (d,  $J$  = 8.6 Hz, 2 H), 7.29 (d,  $J$  = 8.7 Hz, 2 H), 7.33-7.49 (m, 5 H), 7.94 (d,  $J$  = 8.8 Hz, 2 H); Anal. Calcd. for  $C_{37}H_{40}N_6O_6S$ : C, 63.78; H, 5.79; N, 12.06. Found: C, 63.86; H, 5.90; N, 11.92.

**Example 4**

**1,6-Dihydro-5-methoxycarbonyl-1-{N-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]}carboxamido-2-[(4-methoxyphenyl)methyl]thio]-4-methyl-6-(4-nitrophenyl)pyrimidine.**

**a. 4-Methoxycarbonyl-4-phenylpiperidine.** To a stirred solution of  $H_2SO_4$  (16 mL) in MeOH (400 mL), 4-

phenyl-4-piperidinecarboxylic acid 4-methyl  
benzenesulfonate (37.7 g, 0.1 mole) was added and the  
mixture was stirred and refluxed for 8 hours. Excess  
methanol was evaporated at reduced pressure and the  
5 residue was poured into a mixture of ice and 6 N NaOH.  
The pH was adjusted to 10-11 by adding more 6 N NaOH  
and extracted with  $\text{CH}_2\text{Cl}_2$  (3 X 150 mL). The combined  
 $\text{CH}_2\text{Cl}_2$  extracts were dried ( $\text{MgSO}_4$ ) and the solvent  
10 evaporated to leave the desired product as a viscous  
oil. The product (20.2 g, 92%) was used without  
further purification.

**b. 3-(4-Methoxycarbonyl-4-phenylpiperidin-1-yl)propylamine.**

15 A mixture of 4-methoxycarbonyl-4-phenylpiperidine (8.5  
g, 0.039 mol), 3-bromopropylamine hydrobromide (12.7 g,  
0.058 mol), potassium carbonate (13.475 g, 0.0957  
mole), and KI (3.24 g, 0.0195 mol) in 1,4-dioxane (200  
mL) was stirred and refluxed for 24 hours. Dioxane was  
20 evaporated at reduced pressure, the residue was treated  
with ice-cold 6 N NaOH (400 mL) and extracted with  
 $\text{CH}_2\text{Cl}_2$  (4 X 120 mL). Solvent was evaporated from the  
combined dried ( $\text{K}_2\text{CO}_3$ ) extracts and the residue was  
purified by column chromatography on silica gel using  
25  $\text{CHCl}_3/\text{MeOH}/2 \text{ M NH}_3$  in MeOH (20:2:1) as the eluent to  
afford the product as a viscous oil (7.8 g, 72%).

**c. 1,6-Dihydro-5-methoxycarbonyl-1-{N-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]}carbox  
30 amido-2-[(4-methoxyphenyl)methyl]thio}-4-methyl-  
6-(4-nitrophenyl)pyrimidine.** This compound was  
prepared from 1,6-dihydro-5-methoxycarbonyl  
-2-[(4-methoxyphenyl)methyl]thio}-4-methyl-6-(4-nitr  
ophenyl)-1-[(4-nitrophenyl-oxy)carbonyl]pyrimidine (1.0  
35 g, 1.69 mmol), 3-[4-methoxycarbonyl-4-phenyl  
piperidin-1-yl]propylamine (0.56 g, 2.03 mmol, 1.2 eq)  
and purified using similar conditions described in

Example 1 (1.085 g, 88%); m.p. 140-141 °C; <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 1.62-1.74 (m, 2 H), 1.82-2.18 (m, 4 H), 2.21 (s, 3 H), 2.35-2.58 (m, 4 H), 2.75-2.89 (m, 2 H), 3.18-3.30 (m, 1 H), 3.42-3.58 (m, 1 H), 3.61 (s, 3 H), 3.66 (s, 3 H), 3.75 (s, 3 H), 3.91, 4.15 (AB q, *J* = 13.6 Hz, 2 H), 6.14 (s, 1 H), 6.69 (d, *J* = 8.6 Hz, 2 H), 7.02 (d, *J* = 8.6 Hz, 2 H), 7.20-7.37 (m, 7 H), 7.56 (br t, 1 H, NH), 7.90 (d, *J* = 8.8 Hz, 2 H); Anal. Calcd. for C<sub>38</sub>H<sub>43</sub>N<sub>5</sub>O<sub>8</sub>S: C, 62.54; H, 5.94; N, 9.60. Found: C, 62.41; H, 6.06; N, 9.34.

#### Example 5

**5-Methoxycarbonyl-4-methyl-6-(4-nitrophenyl)-1-{N-[3-(4,4-diphenyl-piperidin-1-yl)propyl]}carboxamido-1,2,3,6-tetrahydro-2-thioxo-pyrimidine.**

To a stirred solution of 1,6-dihydro-6-methoxycarbonyl-2-[[{(4-methoxyphenyl)methyl}thio]-4-methyl-6-(4-nitrophenyl)-1-{N-[3-(4,4-diphenylpiperidin-1-yl)propyl]}carboxamidopyrimidine (0.14 g, 0.187 mmol) and ethanethiol (0.5 mL) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) at 5 °C under argon, TFA (0.5 mL) was added and the mixture was allowed to warm to room temperature. After 3 hours, solvents were evaporated completely, the residue was redissolved in EtOAc (10 mL), washed with 5% NaHCO<sub>3</sub> (5 X 1 mL) and dried (MgSO<sub>4</sub>). Solvent was evaporated and the residue was purified by column chromatography using 1:1 hexane/EtOAc to 100% EtOAc as gradient eluent. The oily product was crystallized from hexane and EtOAc (0.096 g, 82%); m.p. 130-131 °C; <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 1.65-1.80 (m, 2 H), 2.31 (s, 3 H), 2.31-2.49 (m, 10 H), 3.25-3.55 (m, 2 H), 3.76 (s, 3 H), 7.01 (s, 1 H), 7.09-7.29 (m, 6 H), 7.41 (d, *J* = 8.2 Hz, 2 H), 8.11 (d, *J* = 8.8 Hz, 2 H), 9.76 (br t, 1 H, NH); Anal. Calcd. for C<sub>34</sub>H<sub>37</sub>N<sub>5</sub>O<sub>6</sub>S.0.3 H<sub>2</sub>O: C, 64.50; H, 5.89; N, 11.06. Found: C, 64.45; H, 6.05; N, 10.87.

#### Example 6

1-{N-[3-(4-(4-Methoxyphenyl)-4-phenylpiperidin-1-yl)propyl]}carboxamido-5-methoxycarbonyl-4-methyl-6-(4-nitrophenyl)-1,2,3,6-tetrahydro-2-thioxo pyrimidine.

5

a. 4-(4-Methoxyphenyl)-4-phenylpiperidine. 4-Hydroxy-4-phenylpiperidine (5.00 g, 28.2 mmol) was added to a suspension of  $\text{AlCl}_3$  (18.8 g, 0.141 mol, 5.00 eq) in anhydrous anisole (100 mL). The mixture was stirred at room temperature for 1 hours and then heated to 50 °C for 3.5 hours. It was cooled to room temperature and poured cautiously into ice-water. The mixture was basified to pH 11 by addition of 6 N aqueous NaOH, and extracted with EtOAc (3 x 75 mL). The combined organic extracts were applied directly to a flash chromatography column, which was eluted with  $\text{CH}_2\text{Cl}_2$ /0.67 M  $\text{NH}_3$  in MeOH (4:1) to afford 1.683 g (22%) of light yellow oil, which was characterized spectroscopically.

b. 3-[4-(4-Methoxyphenyl)-4-phenylpiperidin-1-yl]propionitrile. Acrylonitrile (1.03 mL, 15.7 mmol, 2.50 eq) was added at 0 °C to a solution of 4-(4-methoxyphenyl)-4-phenylpiperidine (1.68 g, 6.28 mmol) in EtOH (20 mL) and the resulting solution was stirred for 1.5 hours at room temperature. After removal of the solvent, the residue was purified by flash chromatography ( $\text{SiO}_2$ , EtOAc- $\text{CHCl}_3$  1:3) to give 1.41 g (70%) of colorless oil, which was characterized spectroscopically.

30

c. 3-[4-(4-Methoxyphenyl)-4-phenylpiperidin-1-yl]propylamine. To a stirred solution of 3-[4-(4-methoxyphenyl)-4-phenylpiperidin-1-yl]propionitrile (1.41 g, 4.40 mmol) in anhydrous THF (10 mL) under argon was added a solution of  $\text{BH}_3$  in THF (1.0 M, 11.0 mL, 2.5 eq) at room temperature. The mixture was refluxed for 4.5 hours and then cooled to room

35

temperature. Aqueous HCl (6 N, 15 mL) was added and stirring was continued for 2 h at 55-60 °C. The mixture was basified to pH 9 by addition of 6 N aq. NaOH and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 75 mL). The combined organic solutions were dried (MgSO<sub>4</sub>) and concentrated. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and treated with HCl in ether (1.0 M, 9.0 mL, 2.0 eq). The solvents were removed, ether (30 mL) was added, the mixture was filtered, and the filter cake was washed with ether (2 x 10 mL). Water (20 mL) was added to the resulting white solid, the pH was adjusted to 10 with 1 N NaOH, and the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 40 mL). The combined organic extracts were dried (MgSO<sub>4</sub>) and concentrated to give 610 mg (43%) of white solid, which was characterized spectroscopically.

**d. 1-{N-[3-(4-(4-Methoxyphenyl)-4-phenylpiperidin-1-yl)propyl]}carboxamido-5-methoxycarbonyl-4-methyl-6-(4-nitrophenyl)-1,2,3,6-tetrahydro-2-thioxopyrimidine.**

To a stirred mixture of 1,6-dihydro-5-methoxycarbonyl-2-[[{(4-methoxyphenyl)methyl}thio]-4-methyl-6-(4-nitrophenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine (0.592 g, 1 mmol) and K<sub>2</sub>CO<sub>3</sub> (0.276 g, 2 mmol) in anhydrous THF (10 mL) at room temperature under argon atmosphere, a solution of 3-[4-(4-methoxyphenyl)-4-phenylpiperidin-1-yl]propylamine (0.390 g, 1.2 mmol, 1.2 eq) in THF (10 mL) was added and the stirring was continued for 1 hour. Solvent was evaporated from the reaction mixture and the residue was redissolved in CH<sub>2</sub>Cl<sub>2</sub> (50 mL), washed with 5% NaHCO<sub>3</sub> (3 X 25 mL), brine (50 mL), and dried (MgSO<sub>4</sub>). The CH<sub>2</sub>Cl<sub>2</sub> solution was filtered and cooled to 5 °C. To this, ethanethiol (0.5 mL) and TFA (0.5 mL) were added and the mixture was stirred and allowed to warm to room temperature. After 3 hours, solvents were evaporated completely, the residue was

redissolved in EtOAc (10 mL), washed with 5% NaHCO<sub>3</sub> (5 X 1 mL), and dried (MgSO<sub>4</sub>). Solvent was evaporated and the residue was purified by column chromatography using 1:1 hexane/EtOAc to 100% EtOAc as gradient eluent. The oily product was crystallized from hexane and EtOAc (0.41 g, 62%); m.p. 120-121 °C; <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 1.60-1.80 (m, 2 H), 2.31 (s, 3 H), 2.31-2.51 (m, 8 H), 3.32-3.43 (m, 2 H), 3.75 (s, 3 H), 3.76 (s, 3 H), 6.77 (d, *J* = 8.8 Hz, 2 H), 7.02 (s, 1 H), 7.12 (d, *J* = 8.6 Hz, 2 H), 7.20-7.27 (m, 6 H), 7.41 (d, *J* = 8.6 Hz, 2 H), 8.11 (d, *J* = 8.8 Hz, 2 H), 9.76 (br t, 1 H, NH); Anal. Calcd. for C<sub>35</sub>H<sub>39</sub>N<sub>5</sub>O<sub>6</sub>S: C, 63.91; H, 5.98; N, 10.65. Found: C, 64.19; H, 6.22; N, 10.36.

#### Example 7

**a. 4-Ethoxycarbonyl-4-phenylpiperidine.** To a stirred solution of H<sub>2</sub>SO<sub>4</sub> (1.62 g, 16.56 mmol) in EtOH (200 mL), 4-phenyl-4-piperidine-carboxylic acid 4-methyl benzenesulfonate (25 g, 66.23 mmol) was added and the mixture was stirred and refluxed for 12 hours. Excess ethanol was evaporated at reduced pressure and the residue was poured into a mixture of ice and 6 N NaOH. The pH was adjusted to 10-11 by adding more 6 N NaOH and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 X 100 mL). The combined CH<sub>2</sub>Cl<sub>2</sub> extracts were dried (MgSO<sub>4</sub>) and the solvent evaporated to leave the desired product as a colorless viscous oil, the <sup>1</sup>H-NMR showed it to be pure (14.68 g, 95%) and was used without any further purification.

#### **b. 3-(4-Ethoxycarbonyl-4-phenylpiperidin-1-yl) propylamine.**

A mixture of 4-ethoxycarbonyl-4-phenylpiperidine (30.5 g, 0.131 mol), 3-bromopropylamine hydrobromide (42.93 g, 0.196 mol), potassium carbonate (36.14 g, 0.241 mole), and KI (10.8 g, 0.065 mol) in 1,4-dioxane (500 mL) was stirred and refluxed for 24 hours. Dioxane was evaporated at reduced pressure, the residue was treated

with ice-cold 6 N NaOH (400 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (4 X 120 mL). Solvent was evaporated from the combined dried (K<sub>2</sub>CO<sub>3</sub>) CH<sub>2</sub>Cl<sub>2</sub> extracts and the residue was purified by column chromatography on silica gel using CHCl<sub>3</sub>/MeOH/2 M NH<sub>3</sub> in MeOH (20:2:1) as the eluent to afford the product as a viscous oil (24.2 g, 83.3%).

c. 1-{N-[3-(4-Ethoxycarbonyl-4-phenylpiperidin-1-yl)propyl]}carboxamido-5-methoxycarbonyl-4-methyl-6-(4-nitrophenyl)-1,2,3,6-tetra-hydro-2-thioxopyrimidine. This compound was prepared from 1,6-dihydro-5-methoxycarbonyl-2-[(4-methoxyphenyl)methyl]thio-4-methyl-6-(4-nitrophenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine (0.592 g, 1 mmol), K<sub>2</sub>CO<sub>3</sub> (0.276 g, 2 mmol), 3-[4-ethoxycarbonyl-4-phenylpiperidin-1-yl]propylamine (0.350 g, 1.2 mmol, 1.2 eq), ethanethiol (0.5 mL), and TFA (0.5 mL) using the procedure described in Example 7 and purified by flash column chromatography (0.295 g, 47%); m.p. 125-126 °C; <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 1.13 (t, J = 7 Hz, 3 H), 1.62-1.80 (m, 2 H), 1.87-2.0 (m, 2 H), 2.06-2.18 (m, 2 H), 2.31 (s, 3 H), 2.34-2.39 (m, 2 H), 2.50-2.55 (m, 2 H), 2.79-2.83 (m, 2 H), 3.30-3.51 (m, 2 H), 3.74 (s, 3 H), 4.07 (q, J = 7 Hz, 2 H), 7.03 (s, 1 H), 7.18-7.36 (m, 6 H), 7.40 (d, J = 8.8 Hz, 2 H), 8.08 (d, J = 8.8 Hz, 2 H), 9.78 (br t, 1 H, NH); Anal. Calcd. for C<sub>31</sub>H<sub>37</sub>N<sub>5</sub>O<sub>7</sub>S: C, 59.70; H, 5.98; N, 11.23. Found: C, 59.55; H, 5.99; N, 11.43.

#### Example 8

1,6-Dihydro-1-{N-[3-(4,4-diphenylpiperidin-1-yl)propyl]}carboxamido-2-methoxy-5-methoxycarbonyl-4-methyl-6-(4-nitrophenyl)pyrimidine. To a stirred mixture of 1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-6-(4-nitrophenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine (0.940 g, 2 mmol) and K<sub>2</sub>CO<sub>3</sub> (0.552 g, 4 mmol) in anhydrous THF (20 mL) at room temperature under argon atmosphere, a solution of 3[4,4-diphenylpiperidin-1-yl]

propylamine (0.882 g, 3 mmol, 1.5 eq) in THF (5 mL) was added and the stirring was continued for 1 hour. Solvent was evaporated from the reaction mixture, the residue was redissolved in CH<sub>2</sub>Cl<sub>2</sub> (50 mL), washed with 5% NaHCO<sub>3</sub> (3 X 25 mL), brine (50 mL), and dried (MgSO<sub>4</sub>). Solvent was evaporated and the residue was purified by flash chromatography on silica gel using 10% methanol in EtOAc as the eluent to give the desired product as an oil, which on trituration with hexane and drops of EtOAc became a white powder (1.10 g, 88%); m.p. 95-96 °C; <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 1.61-1.71 (m, 2 H), 2.26-2.33 (m, 2 H), 2.38 (s, 3 H), 2.39-2.50 (m, 8 H), 3.20-3.41 (m, 2 H), 3.65 (s, 3 H), 3.89 (s, 3 H), 6.65 (s, 1 H), 6.84 (br t, 1 H, NH), 7.08-7.29 (m, 10 H), 7.40 (d, J = 8.7 Hz, 2 H), 8.03 (d, J = 8.6 Hz, 2 H); Anal. Calcd. for C<sub>35</sub>H<sub>39</sub>N<sub>5</sub>O<sub>6</sub>.0.75 CH<sub>2</sub>Cl<sub>2</sub>: C, 62.28; H, 5.92; N, 10.16. Found: C, 62.23; H, 5.76; N, 10.12.

#### Example 9

**5-Methoxycarbonyl-4-methyl-6-(4-nitrophenyl)-1-{N-[3-(4,4-diphenyl-piperidin-1-yl)propyl]}carboxamido-2-oxo-1,2,3,6-tetrahydropyrimidine.**

a

**1,6-Dihydro-5-methoxycarbonyl-2-methoxy-4-methyl-6-(4-nitro-phenyl)pyrimidine.**

A mixture of methyl 2-{(4-nitrophen-yl)methylene}-3-oxobutyrate (12.46 g, 0.05 mol), O-methylisourea hydrogen sulfate (10.32 g, 0.06 mol), and NaOAc (9.84 g, 0.06 mol) in DMF (50 mL) was stirred and heated at 70-75 °C for 4 hours. The mixture was cooled and poured into ice-water (300 mL). The precipitate formed was filtered, washed with water, and dried. The crude product was purified by flash column chromatography on silica gel using 10% through 30% EtOAc in hexane as the gradient eluent (9.8 g, 64%). The <sup>1</sup>H-NMR analysis of the product showed it to be a 19:1 mixture of the



amine/imine tautomers which was used as such in the next step. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 2.32, 2.38 (2 s, 3 H), 3.59, 3.70 (2 s, 3 H), 3.70, 3.85 (2 s, 3 H), 5.40, 5.66 (s, d, J = 3 Hz, 1 H), 5.50, 6.08 (s, d, J = 3 Hz, 1 H), 7.43, 7.45 (2 d, J = 9 Hz, 2 H), 8.10, 8.11 (2 d, J = 9 Hz, 2 H).

**b. 1,6-Dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-6-(4-nitrophenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine.**

To a well-stirred mixture of 1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-6-(4-nitrophenyl)pyrimidine (5.7 g, 0.0187 mol), NaHCO<sub>3</sub> (6.27 g, 0.074 mol), CH<sub>2</sub>Cl<sub>2</sub> (200 mL), and water (50 mL) at 0-5 °C, 4-nitrophenyl chloroformate (3.76 g, 0.0186 mol) was added in 5 min and the mixture was allowed to warm to room temperature. After 10 hours, the TLC analysis of the reaction mixture showed the presence of a small amount of starting pyrimidine, therefore, more 4-nitrophenyl chloroformate (0.65 g, 0.0032 mol) was added and the stirring continued for an additional 4 hours. The two layers were separated, the CH<sub>2</sub>Cl<sub>2</sub> layer was washed with saturated aqueous NaHCO<sub>3</sub> solution (3 X 50 mL), dried (MgSO<sub>4</sub>), and the solvent evaporated. The residue was recrystallized from CH<sub>2</sub>Cl<sub>2</sub> and hexane to give the product as white crystals (12.8 g, 89%); <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 2.48 (s, 3 H), 3.69 (s, 3 H), 3.94 (s, 3 H), 6.34 (s, 1 H), 7.36 (d, J = 9.1 Hz, 2 H), 7.46 (d, J = 8.7 Hz, 2 H), 8.14 (d, J = 8.7 Hz, 2 H), 8.26 (d, J = 9.1 Hz, 2 H); m.p. 168-169 °C. Anal. Calcd. for C<sub>21</sub>H<sub>18</sub>N<sub>4</sub>O<sub>9</sub>: C, 53.62; H, 3.86; N, 11.91. Found: C, 53.69; H, 3.92; N, 11.85.

**c. 5-Methoxycarbonyl-4-methyl-6-(4-nitrophenyl)-1-{N-[3-(4,4-di-phenylpiperidin-1-yl)propyl]}carboxamido-2-oxo-1,2,3,6-tetrahydro-pyrimidine.**

To a stirred solution of 1,6-dihydro-2-methoxy-6-

methoxycarbonyl-4-methyl-6-(4-nitrophenyl)-1-{N-[3-(4,4-diphenylpiperidin-1-yl)propyl]}carboxamidopyrimidine (0.208 g, 0.33 mmol) in THF (10 mL) at 5 °C under argon, 3 N HCl (6 mL) was added and the mixture was allowed to warm to room temperature. After 2 hours, solvents were evaporated completely, the residue was treated with 40 mL of 10% NaHCO<sub>3</sub>, the product was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 X 15 mL) and the combined extracts were dried (MgSO<sub>4</sub>). Solvent was evaporated and the residue was crystallized from hexane and EtOAc (0.20 g, 97%); m.p. 197-198 °C; <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 1.63-1.67 (m, 2 H), 2.23-2.28 (m, 2 H), 2.34 (s, 3 H), 2.37-2.42 (m, 8 H), 3.20-3.41 (m, 2 H), 3.69 (s, 3 H), 6.75 (s, 1 H), 7.08-7.26 (m, 11 H), 7.46 (d, J = 8.7 Hz, 2 H), 8.08 (d, J = 8.7 Hz, 2 H), 8.77 (br t, 1 H, NH); Anal. Calcd. for C<sub>34</sub>H<sub>37</sub>N<sub>5</sub>O<sub>6</sub>: C, 66.76; H, 6.10; N, 11.45. Found: C, 66.48; H, 5.97; N, 11.25.

#### Example 10

1-{N-[3-(4-(4-Methoxyphenyl)-4-phenylpiperidin-1-yl)propyl]}carboxamido-5-methoxycarbonyl-4-methyl-6-(4-nitrophenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine. To a stirred mixture of 1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-6-(4-nitrophenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine (0.47 g, 1 mmol) and K<sub>2</sub>CO<sub>3</sub> (0.552 g, 4 mmol) in anhydrous THF (10 mL) at room temperature under argon atmosphere, a solution of 3-[4-(4-methoxyphenyl)-4-phenylpiperidin-1-yl]propyl-amine (0.390 g, 1.2 mmol, 1.2 eq) in THF (10 mL) was added and the stirring was continued for 2 hours. The solid was removed by filtration and the solution was cooled to 0-5 °C. 6N HCl (2 mL) was added to the solution and stirring was continued. After 3 hours, solvents were evaporated completely, the residue was redissolved in CH<sub>2</sub>Cl<sub>2</sub> (20 mL), washed with 10% NaHCO<sub>3</sub> (2 X 10 mL), and dried (MgSO<sub>4</sub>). Solvent was evaporated and the residue was purified by column

chromatography using 1:1 hexane/EtOAc to 100% EtOAc as gradient eluent. The oily product was crystallized from hexane and EtOAc (0.55 g, 86%); m.p. 100-102 °C; <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 1.65-1.80 (m, 2 H), 2.26-2.31 (m, 2 H), 2.35 (s, 3 H), 2.39-2.44 (m, 6 H), 3.18-3.40 (m, 2 H), 3.69 (s, 3 H), 3.73 (s, 3 H), 6.75 (s, 1 H), 7.60 (d, J = 8.7 Hz, 2 H), 6.84 (br s, 1 H, NH), 7.10 (d, J = 8.7 Hz, 2 H), 7.18-7.26 (m, 5 H), 7.46 (d, J = 8.6 Hz, 2 H), 8.08 (d, J = 8.6 Hz, 2 H), 8.78 (br t, 1 H, NH); Anal. Calcd. for C<sub>35</sub>H<sub>39</sub>N<sub>5</sub>O<sub>7</sub>·0.12 CH<sub>2</sub>Cl<sub>2</sub>·0.12 EtOAc: C, 64.54; H, 6.12; N, 10.57. Found: C, 64.44; H, 6.12; N, 10.28.

#### Example 11

1-{N-[3-(4-Methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]}carboxamido-5-methoxycarbonyl-4-methyl-6-(4-nitrophenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine (Scheme 2).

To a stirred mixture of 1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-6-(4-nitrophenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine (0.47 g, 1 mmol), K<sub>2</sub>CO<sub>3</sub> (0.276 g, 2 mmol) in anhydrous THF (10 mL) at room temperature under argon atmosphere, a solution of 3-[4-methoxycarbonyl-4-phenylpiperidin-1-yl]propylamine (0.332 g, 1.2 mmol, 1.2 eq) in THF (10 mL) was added and the stirring was continued for 2 hours. The solid was removed by filtration and the solution was cooled to 0-5 °C. To this, 6 N HCl (2 mL) was added and the stirring continued. After 3 hours, solvents were evaporated completely, the residue was redissolved in CH<sub>2</sub>Cl<sub>2</sub> (20 mL), washed with 10% NaHCO<sub>3</sub> (2 X 10 mL), and dried (MgSO<sub>4</sub>). Solvent was evaporated and the residue was purified by column chromatography using 1:1 hexane/EtOAc to 100% EtOAc as gradient eluent. The oily product was crystallized from hexane and EtOAc (0.55 g, 86%); m.p. 180-181 °C; <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 1.60-1.80 (m, 2 H), 1.85-1.95 (m, 2 H), 2.03-2.10 (m, 2 H),

2.28-2.33 (m, 2 H), 2.35 (s, 3 H), 2.48-2.50 (m, 2 H),  
3.20-3.40 (m, 2 H), 3.60 (s, 3 H), 3.68 (s, 3 H), 6.75  
(s, 1 H), 7.20-7.34 (m, 6 H), 7.46 (d,  $J = 8.8$  Hz, 2  
H), 8.07 (d,  $J = 8.8$  Hz, 2 H), 8.78 (br t, 1 H, NH);  
5 Anal. Calcd. for  $C_{30}H_{35}N_5O_8$ : C, 60.70; H, 5.94; N, 11.80.  
Found: C, 60.71; H, 5.99; N, 11.43.

**Examples 11a & 11 b**

(+)-1-{N-[3-(4-Methoxycarbonyl-4-phenylpiperidin-1-yl)  
10 propyl]}carboxamido-5-methoxycarbonyl-4-methyl-6-  
(4-nitrophenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine and  
(-)-1-{N-[3-(4-Methoxycarbonyl-4-phenylpiperidin-1-yl)  
propyl]}carboxamido-5-methoxycarbonyl-4-methyl-6-(4-  
15 nitrophenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine (Scheme  
3).

a. (-)-1,6-Dihydro-2-methoxy-5-methoxycarbonyl-4-  
methyl-6-(4-nitro-phenyl)-1-{N-[(2-phenyl)ethyl]}  
carboxamidopyrimidine and (+)-1,6-Dihydro-2-methoxy-5-  
20 methoxycarbonyl-4-methyl-6-(4-nitrophenyl)-1-{N-[(2-  
phenyl)ethyl]}carboxamidopyrimidine.

To a stirred solution of ( $\pm$ )-1,6-dihydro-2-methoxy-5-  
methoxycarbonyl-4-methyl-6-(4-nitrophenyl)-1-[(4-nitr  
ophenyloxy)carbonyl]pyrimidine (2.66 g, 5.6 mmol) in  
25 anhydrous THF (80 mL) at room temperature under argon  
atmosphere, a solution of (S)-(-)- $\alpha$ -methylbenzylamine  
(0.82 g, 6.78 mmol, 1.2 eq) in THF (5 mL) was added and  
the stirring was continued for 6 hours. Solvent was  
evaporated from the reaction mixture, the residue was  
30 redissolved in  $CH_2Cl_2$  (50 mL), washed with 5%  $NaHCO_3$  (3  
X 25 mL), brine (50 mL), and dried ( $MgSO_4$ ). Solvent was  
evaporated and the residue was purified by flash  
chromatography on silica gel using 5% to 30% EtOAc in  
hexane as the gradient eluent. The first major product  
35 to elute was (-)-1,6-dihydro-2-methoxy-5-methoxy  
carbonyl-4-methyl-6-(4-nitrophenyl)-1-{N-[(2-phenyl)  
ethyl]}carboxamidopyrimidine and this compound was

crystallized from isopropyl ether (0.85 g, 33.6%); m.p. 119-120 °C;  $[\alpha]_D = -329.32$  ( $\text{CH}_2\text{Cl}_2$ , 10.3 g/100 mL);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  1.47 (d,  $J = 7$  Hz, 3 H), 2.40 (s, 3 H), 3.61 (s, 3 H), 3.95 (s, 3 H), 4.96 (quint,  $J = 6.5$  Hz, 2 H), 6.66 (s, 1 H), 6.82 (d,  $J = 6.8$  Hz, 1 H, NH), 7.22-7.36 (m, 5 H), 7.43 (d,  $J = 8.6$  Hz, 2 H), 8.09 (d,  $J = 8.6$  Hz, 2 H); Anal. Calcd. for  $\text{C}_{23}\text{H}_{24}\text{N}_4\text{O}_6$ : C, 61.06; H, 5.35; N, 12.38. Found: C, 60.85; H, 5.13; N, 12.42. The second major compound to elute was (+)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-6-(4-nitrophenyl)-1-{N-[(2-phenyl)ethyl]}carboxamido pyrimidine and this compound was crystallized from isopropyl ether (0.92 g, 36.4%); m.p. 138-140 °C;  $[\alpha]_D = +171.81$  ( $\text{CH}_2\text{Cl}_2$ , 11.31 g/100 mL);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  1.47 (d,  $J = 7$  Hz, 3 H), 2.42 (s, 3 H), 3.644 (s, 3 H), 3.917 (s, 3 H), 4.989 (quint,  $J = 6.5$  Hz, 2 H), 6.70 (s, 1 H), 6.81 (d,  $J = 6.8$  Hz, 1 H, NH), 7.22-7.35 (m, 5 H), 7.36 (d,  $J = 8.6$  Hz, 2 H), 8.04 (d,  $J = 8.6$  Hz, 2 H); Anal. Calcd. for  $\text{C}_{23}\text{H}_{24}\text{N}_4\text{O}_6$ : C, 61.06; H, 5.35; N, 12.38. Found: C, 60.95; H, 5.20; N, 12.38.

**b. (+)-1-{N-[3-(4-Methoxycarbonyl-4-phenyl piperidin-1-yl)propyl]}carboxamido-5-methoxycarbonyl-4-methyl-6-(4-nitrophenyl)-2-oxo-1,2,3,6-tetrahydro pyrimidine.**

A solution of (+)-1,6-dihydro-2-methoxy-5-methoxy carbonyl-4-methyl-6-(4-nitrophenyl)-1-{N-[(2-phenyl) ethyl]}carboxamidopyrimidine (0.226 g, 0.5 mmol) and 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) (0.076 g, 0.5 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 mL) was stirred and refluxed for 4 hours and the solvent evaporated. The product was purified by column chromatography using 30% EtOAc in hexane as the eluent. The product was found to be a mixture of the amine-imine tautomers (0.120 g, 78.7%);  $[\alpha]_D = +14.5$  ( $\text{CH}_2\text{Cl}_2$ , 6 g/100 mL).

To a well-stirred solution of (+)-1,6-dihydro-5-methoxy

carbonyl-2-methoxy-4-methyl-6-(4-nitrophenyl)pyrimidine (0.12 g, 0.393 mmol) and pyridine (0.5 mL) in  $\text{CH}_2\text{Cl}_2$  (10 mL) at 0-5 °C, 4-nitrophenyl chloroformate (0.095 g, 0.472 mmol) was added in 5 min and the mixture was allowed to warm to room temperature. After 2 h, saturated aqueous  $\text{NaHCO}_3$  solution (10 mL) was added and the stirring continued for 30 min. The two layers were separated, the  $\text{CH}_2\text{Cl}_2$  layer was washed with saturated aqueous  $\text{NaHCO}_3$  solution (3 X 5 mL), dried ( $\text{Na}_2\text{SO}_4$ ), and the solvent evaporated. The residue was redissolved in THF (10 mL) and mixed with  $\text{K}_2\text{CO}_3$  (0.11 g, 0.8 mmol). To this, a solution of 3-[4-methoxycarbonyl-4-phenyl piperidin-1-yl]propylamine (0.138 g, 0.5 mmol) in THF (5 mL) was added and the mixture was stirred for 2 hours. The solid was removed by filtration and the solution was cooled to 0-5 °C. To this, 6 N HCl (0.5 mL) was added and the stirring continued. After 3 hours, solvents were evaporated completely, the residue was redissolved in  $\text{CH}_2\text{Cl}_2$  (20 mL), washed with 10%  $\text{NaHCO}_3$  (4 X 5 mL), and dried ( $\text{MgSO}_4$ ). Solvent was evaporated and the residue was purified by column chromatography using 1:1 hexane/EtOAc to 100% EtOAc as gradient eluent. The oily product was crystallized from hexane and EtOAc (0.19 g, 82%); m.p. 138-140 °C;  $[\alpha]_D = +108$  ( $\text{CH}_2\text{Cl}_2$ , 6.65 g/100 mL);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  1.60-1.80 (m, 2 H), 1.85-1.95 (m, 2 H), 2.03-2.10 (m, 2 H), 2.28-2.33 (m, 2 H), 2.35 (s, 3 H), 2.48-2.50 (m, 2 H), 3.20-3.40 (m, 2 H), 3.60 (s, 3 H), 3.68 (s, 3 H), 6.75 (s, 1 H), 7.20-7.34 (m, 5 H), 7.46 (d,  $J = 8.8$  Hz, 2 H), 7.60 (br s, 1 H, NH), 8.07 (d,  $J = 8.8$  Hz, 2 H), 8.78 (br t, 1 H, NH); Anal. Calcd. for  $\text{C}_{30}\text{H}_{35}\text{N}_5\text{O}_8 \cdot 0.2 \text{CH}_2\text{Cl}_2 \cdot 0.2 \text{EtOAc}$ : C, 59.27; H, 5.94; N, 11.15. Found: C, 59.07; H, 5.76; N, 10.99.

c. (-)-1-{N-[3-(4-Methoxycarbonyl-4-phenyl piperidin-1-yl)propyl]}carboxamido-5-methoxy carbonyl-4-methyl-6-(4-nitrophenyl)-2-oxo-

**1,2,3,6-tetrahydropyrimidine.**

A solution of (-)-1,6-dihydro-2-methoxy-5-methoxy carbonyl-4-methyl-6-(4-nitrophenyl)-1-{N-[(2-phenyl) ethyl]}carboxamidopyrimidine (0.35 g, 0.774 mmol) and  
5 1,8-diazabicyclo[5.4.0]-unde-7-ene (DBU) (0.117 g, 0.774 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was stirred and refluxed for 8 hours and the solvent evaporated. The product was purified by column chromatography using 30% EtOAc in hexane as the eluent. The product, (-)-  
10 1,6-dihydro-5-methoxycarbonyl-2-methoxy-4-methyl-6-(4-nitrophenyl)pyrimidine, was found to be a mixture of the amine-imine tautomers (0.170 g, 72%). To a well-stirred solution of (-)-1,6-dihydro-5-methoxy carbonyl-2-methoxy-4-methyl-6-(4-nitrophenyl)pyrimidine  
15 (0.152 g, 0.5 mmol) and pyridine (0.5 mL) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) at 0-5 °C, 4-nitrophenyl chloroformate (0.121 g, 0.6 mmol) was added in 5 min and the mixture was allowed to warm to room temperature. After 2 hours, saturated aqueous NaHCO<sub>3</sub> solution (10 mL) was added and the stirring continued for 30 min. The two layers were  
20 separated, the CH<sub>2</sub>Cl<sub>2</sub> layer was washed with saturated aqueous NaHCO<sub>3</sub> solution (3 X 5 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and the solvent evaporated. The residue was redissolved in THF (10 mL) and mixed with K<sub>2</sub>CO<sub>3</sub> (0.165 g, 1.2 mmol). To this, a solution of 3-[4-methoxycarbonyl-4-phenylpiperidin-1-yl]propylamine (0.166 g, 0.6 mmol)  
25 in THF (5 mL) was added and the mixture was stirred for 2 hours. The solid was removed by filtration and the solution was cooled to 0-5 °C. To this, 6 N HCl (0.5 mL) was added and the stirring continued. After 3 hours, solvents were evaporated completely, the residue was redissolved in CH<sub>2</sub>Cl<sub>2</sub> (20 mL), washed with 10% NaHCO<sub>3</sub> (4 X 5 mL), and dried (MgSO<sub>4</sub>). Solvent was  
30 evaporated and the residue was purified by column chromatography using 1:1 hexane/EtOAc to 100% EtOAc as gradient eluent. The oily product was crystallized from hexane and EtOAc (0.19 g, 64%); m.p. 138-140 °C;  
35

$[\alpha]_D = -106$  ( $\text{CH}_2\text{Cl}_2$ , 3.95 g/100 mL);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  1.60-1.80 (m, 2 H), 1.85-1.95 (m, 2 H), 2.03-2.10 (m, 2 H), 2.28-2.33 (m, 2 H), 2.35 (s, 3 H), 2.48-2.50 (m, 2 H), 3.20-3.40 (m, 2 H), 3.60 (s, 3 H), 3.68 (s, 3 H), 6.75 (s, 1 H), 7.20-7.34 (m, 6 H), 7.46 (d,  $J = 8.8$  Hz, 2 H), 8.07 (d,  $J = 8.8$  Hz, 2 H), 8.78 (br t, 1 H, NH); Anal. Calcd. for  $\text{C}_{30}\text{H}_{35}\text{N}_5\text{O}_8 \cdot 0.4 \text{ CH}_2\text{Cl}_2$ : C, 58.18; H, 5.75; N, 11.16. Found: C, 58.25; H, 5.67; N, 10.98.

10 **Example 12**

**5-Methoxycarbonyl-1-{N-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]}carboxamido-4-methyl-6-(3,4-methylenedioxyphenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine.**

15 To a stirred solution of 5-benzyloxycarbonyl-1-{N-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]}carboxamido-4-methyl-6-(3,4-methylenedioxyphenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine (0.320 g, 0.48 mmol) in methanol (20 mL) and  $\text{HCOOH}$  (1 mL) at 0-5 °C, 10% Pd-C (0.26 g) was added in portions and the cooling bath was removed. TLC analysis of the reaction mixture at frequent intervals showed the completion of the reaction after 2 hours. The catalyst was removed by filtration and the solvent was evaporated to leave

20 1-{N-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]}carboxamido-4-methyl-6-(3,4-methylenedioxyphenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine-5-carboxylic acid as a white solid (0.275 g, 99%). The product was used in the next step without any further purification and characterization. A mixture of 1-{N-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]}carboxamido-4-methyl-6-(3,4-methylenedioxyphenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine-5-carboxylic acid (0.2 g, 0.346 mmol), 1-(3-dimethylamino propyl)-3-ethylcarbodiimide hydrochloride (0.382 g, 2 mmol), and 4-(N,N-dimethylamino)pyridine (0.488 g, 4 mmol), in methanol (20 mL) was stirred and refluxed for

30

35



5 h and the solvent evaporated. The residue was redissolved in  $\text{CH}_2\text{Cl}_2$  (15 mL), washed with saturated aqueous ammonium chloride solution (3 X 10 mL), and dried ( $\text{Na}_2\text{SO}_4$ ). Evaporation of the solvent left the pure product as white powder (0.202 g, 99%); m.p. 139-141 °C;  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  1.62-1.80 (m, 2 H), 1.95-2.20 (m, 4 H), 2.35 (s, 3 H), 2.30-2.55 (m, 4 H), 2.76-2.90 (m, 2 H), 3.21-3.40 (m, 2 H), 3.61 (s, 3 H), 3.67 (s, 3 H), 5.89 (s, 2 H), 6.61-6.82 (m, 3 H), 6.63 (s, 1 H), 7.21-7.35 (m, 6 H), 8.79 (br t, 1 H, NH); Anal. Calcd. for  $\text{C}_{31}\text{H}_{36}\text{N}_4\text{O}_8 \cdot 0.3 \text{ EtOAc}$ : C, 62.47; H, 6.25; N, 9.05. Found: C, 62.64; H, 6.25; N, 8.87.

### Example 13

(+)-5-Carboxamido-4-ethyl-1-{N-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]}carboxamido-6-(4-nitrophenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine (Scheme 4).

a. 2-Cyanoethyl 3-{(4-nitrophenyl)methylene}-4-oxopentanoate.

A mixture of ethyl propionylacetate (25 g, 0.173 mol) and 3-hydroxypropionitrile (18.48 g, 0.26 mol) was stirred and heated at 200-205 °C for 2 h and the ethanol formed was removed by distillation. The residue was subjected to high vacuum distillation and the fraction distilling at 120-125 °C at 0.4 mm of Hg was collected to get 2-cyanoethyl propionylacetate (21.5 g, 73.4%).

A mixture of 4-nitrobenzaldehyde (14.46 g, 0.957 mol), 2-cyanoethyl propionylacetate (17.0 g, 0.1005 mol), piperidine (0.41 g, 476 mL, 4.8 mmol), and acetic acid (0.288 g, 274 mL, 4.8 mmol) in 2-propanol (400 mL) was stirred at room temperature for 24 h. The white solid, 2-cyanoethyl 3-{(4-nitrophenyl)methylene}-4-oxopentanoate, formed was filtered, washed with 2-propanol (2 X 50 mL) and dried (28.34 g, 97%); m.p. 98-100 °C.

**b. 5-(2-Cyanoethoxycarbonyl)-1,6-dihydro-2-methoxy-4-ethyl-6-(4-nitrophenyl)pyrimidine.**

5 A mixture of 2-cyanoethyl 3-{(4-nitrophenyl)methylene}  
-4-oxopentanoate (5.00 g, 16.54 mmol), O-methylisourea  
hydrogen sulfate (3.422 g, 19.85 mmol), and NaHCO<sub>3</sub> (2.78  
g, 33.08 mol) in EtOH (70 mL) was stirred and heated at  
85-90 °C for 5 h. The solid was removed by filtration  
and ethanol was evaporated from the filtrate. The  
10 residue was redissolved in EtOAc (300 mL), washed with  
water (2 X 100 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and the solvent  
evaporated. The crude product was purified by flash  
column chromatography on silica gel using CHCl<sub>3</sub>/methanol  
(30:1) as the eluent, to leave the product as a white  
15 solid (2.95 g, 50%). The <sup>1</sup>H-NMR analysis of the product  
showed it to be a 5:1 mixture of the amine/imine  
tautomers and was used as such in the next step.

**c. 5-(2-Cyanoethoxycarbonyl)-4-ethyl-1,6-dihydro-2-methoxy-6-(4-nitrophenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine.**

To a well-stirred solution of 5-(2-cyanoethoxy  
carbonyl)-4-ethyl-1,6-dihydro-2-methoxy-6-  
25 (4-nitrophenyl)pyrimidine (2.64 g, 7.36 mmol) and  
pyridine (1.19 mL, 14.72 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) at 0-5  
°C, 4-nitrophenyl chloroformate (1.485 g, 7.36 mmol) was  
added in 5 min and the mixture was allowed to warm to  
room temperature. After 16 h, saturated aqueous NaHCO<sub>3</sub>  
30 solution (25 mL) was added and the stirring continued  
for 30 min. The two layers were separated, the CH<sub>2</sub>Cl<sub>2</sub>  
layer was washed with saturated aqueous NaHCO<sub>3</sub> solution  
(3 X 50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and the solvent evaporated.  
The crude product was purified by flash column  
35 chromatography on silica gel using CHCl<sub>3</sub>/EtOAc (25:1) as  
the eluent to give the product as a viscous oil (1.70  
g, 44%); <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 1.24 (t, J = 7 Hz, 3 H),

2.61-2.68 (m, 2 H), 2.88-2.92 (m, 2 H), 3.97 (s, 3 H), 4.32 (t,  $J = 7$  Hz, 2 H), 6.34 (s, 1 H), 7.37 (d,  $J = 9.2$  Hz, 2 H), 7.50 (d,  $J = 8.7$  Hz, 2 H), 8.18 (d,  $J = 8.7$  Hz, 2 H), 8.28 (d,  $J = 9.2$  Hz, 2 H).

5

**d. 5-(2-Cyanoethoxycarbonyl)-4-ethyl-1,6-dihydro-2-methoxy-6-(4-nitrophenyl)-1-{N-[(2-phenyl)ethyl]}carboxamidopyrimidine.**

To a stirred solution of 5-(2-cyanoethoxycarbonyl)-4-ethyl-1,6-dihydro-2-methoxy-6-(4-nitrophenyl)-1-  
 10 [(4-nitrophenyloxy)carbonyl]pyrimidine (17.5 g, 33.43 mmol) in anhydrous THF (200 mL) at room temperature under argon atmosphere, (R)-(+)- $\alpha$ -methylbenzylamine (4.86 g, 40.11 mmol) was added and the stirring was  
 15 continued for 16 h. Solvent was evaporated from the reaction mixture and the residue was purified by flash chromatography on silica gel using toluene/EtOAc (20:3) as the eluent. The first major product to elute was (+)-5-(2-cyanoethoxycarbonyl)-4-ethyl-1,6-dihydro-2-methoxy-6-(4-nitrophenyl)-1-{N-[(2-phenyl)ethyl]}  
 20 carboxamidopyrimidine and obtained as a viscous oil (6.11 g, 36.2%);  $[\alpha]_D = +299.5$  ( $c = 1.95$ ,  $\text{CHCl}_3$ );  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  1.18 (t,  $J = 7$  Hz, 3 H), 1.47 (d,  $J = 7$  Hz, 3 H), 2.61 (t, 2 H), 2.7-2.92 (m, 2 H), 3.98 (s, 3 H), 4.20-4.32 (m, 2 H), 4.96 (quint,  $J = 6.5$  Hz, 2 H), 6.66 (s, 1 H), 6.82 (d,  $J = 6.8$  Hz, 1 H, NH), 7.22-7.36 (m, 5 H), 7.45 (d,  $J = 8.6$  Hz, 2 H), 8.11 (d,  $J = 8.6$  Hz, 2 H). The second major compound to elute was (-)-5-(2-cyanoethoxycarbonyl)-4-ethyl-1,6-dihydro-2-methoxy-6-(4-nitrophenyl)-1-{N-[(2-phenyl)ethyl]}  
 30 carboxamidopyrimidine and obtained as a viscous oil (5.92 g, 35%);  $[\alpha]_D = -105.1$  ( $c = 3.9$ ,  $\text{CHCl}_3$ );  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  1.20 (t,  $J = 7$  Hz, 3 H), 1.48 (d,  $J = 7$  Hz, 3 H), 2.62 (t, 2 H), 2.82 (q, 2 H), 3.94 (s, 3 H), 4.20-4.32 (m, 2 H), 4.96 (quint,  $J = 6.5$  Hz, 2 H), 6.69 (s, 1 H), 6.84 (d,  $J = 6.8$  Hz, 1 H, NH), 7.22-7.36 (m, 5 H), 7.39 (d,  $J = 8.6$  Hz, 2 H), 8.06 (d,  $J = 8.6$  Hz, 2 H).

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2 H).

**e. (+)-5-(2-Cyanoethoxycarbonyl)-1,6-dihydro-2-methoxy-4-ethyl-6-(4-nitrophenyl)pyrimidine.**

5 To a stirred solution of (+)-5-(2-cyanoethoxycarbonyl)-4-ethyl-1,6-dihydro-2-methoxy-6-(4-nitrophenyl)-1-{N-[(2-phenyl)ethyl]}carboxamido  
pyrimidine (2.62 g, 5.182 mmol) in toluene (40 mL) was  
10 added 1,8-diazabicyclo[5,4,0]-undec-7-ene (0.237, 1.55 mmol) at room temperature and the resulting solution  
was heated at 90 °C for 3.5 minutes. The solvent was  
evaporated and the residue was purified by flash column  
chromatography on silica gel using 9:1 CHCl<sub>3</sub>/EtOAc as  
the eluent, to give 1.32 g (71%) of (+)-5-(2-  
15 cyanoethoxycarbonyl)-1,6-dihydro-2-methoxy-4-ethyl-6-(4-nitrophenyl)pyrimidine;  $[\alpha]_D = +4.0$  (c = 3.25, CHCl<sub>3</sub>).

**f. (+)-5-(2-Cyanoethoxycarbonyl)-4-ethyl-1,6-dihydro-2-methoxy-6-(4-nitrophenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine.**

To a well-stirred solution of 5-(2-cyanoethoxycarbonyl)-  
25 -4-ethyl-1,6-dihydro-2-methoxy-6-(4-nitrophenyl)  
pyrimidine (1.62 g, 4.52 mmol) and 4-(N,N-dimethylamino)pyridine (0.663 g, 5.43 mmol) in CH<sub>2</sub>Cl<sub>2</sub>  
(50 mL) at 0-5 °C, 4-nitrophenyl chloroformate (1.094 g,  
5.43 mmol) was added in 5 minutes and the mixture was  
30 allowed to warm to room temperature. After 3 hours the  
solvent evaporated and the product was purified by  
flash column chromatography on silica gel using  
CHCl<sub>3</sub>/EtOAc (25:1) as the eluent to give the product as  
a white solid (2.25 g, 95%); <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 1.24 (t,  
35 J = 7 Hz, 3 H), 2.61-2.68 (m, 2 H), 2.88-2.92 (m, 2 H),  
3.97 (s, 3 H), 4.32 (t, J = 7 Hz, 2 H), 6.34 (s, 1 H),  
7.37 (d, J = 9.2 Hz, 2 H), 7.50 (d, J = 8.7 Hz, 2 H),  
8.18 (d, J = 8.7 Hz, 2 H), 8.28 (d, J = 9.2 Hz, 2 H);

$[\alpha]_D = +317.2$  ( $c = 3.9$ ,  $\text{CHCl}_3$ ).

g. (+)-5-(2-Cyanoethoxycarbonyl)-4-ethyl-1-{N-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]}  
5 carboxamido-6-(4-nitrophenyl)-2-oxo-1,2,3,6-tetrahydro  
pyrimidine.

To a stirred mixture of (+)-5-(2-cyanoethoxycarbonyl)-  
-4-ethyl-1,6-dihydro-2-methoxy-6-(4-nitrophenyl)  
10 -1-[(4-nitrophenyloxy)carbonyl]pyrimidine (3.60 g,  
6.878 mmol) in anhydrous THF (100 mL) at room  
temperature under argon atmosphere, a solution of 3-[4-  
methoxycarbonyl-4-phenylpiperidin-1-yl]propylamine  
15 (2.47 g, 8.94 mmol, 1.3 eq) in THF (10 mL) was added  
and the stirring was continued for 12 hours. The  
mixture was cooled to 0 °C and aqueous 6N hydrochloric  
acid (10 mL). The mixture was allowed to warm to room  
temperature and the stirring was continued for 5 h.  
Solvent was evaporated from the reaction mixture, the  
20 residue was purified by flash chromatography on silica  
gel using ethyl acetate (800 mL) followed by  
chloroform-methanol-2M ammonia in methanol (90/8/4) as  
the eluent, to obtain the desired product as a white  
powder (4.40 g, 98.5%);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  1.23 (t,  $J =$   
25 7.5 Hz, 3 H), 2.0-2.1 (m, 2 H), 2.40-2.95 (m, 12 H),  
3.25-3.50 (m, 4 H), 3.65 (s, 3 H), 4.27-4.32 (m, 2 H),  
6.64 (s, 1 H), 7.20-7.33 (m, 5 H), 7.49 (d,  $J = 7.8$  Hz,  
2 H), 8.08 (d,  $J = 7.8$  Hz, 2 H), 8.70-8.90 (m, 2 H);  
[ $\alpha$ ] $_D = +112.1$  ( $c = 2.15$ ,  $\text{CHCl}_3$ ); This product was used  
30 in the next step without any additional analysis.

h. (+)-5-Carboxamido-4-ethyl-1-{N-[3-(4-methoxycarbonyl-  
4-phenylpiperidin-1-yl)propyl]}carboxamido-6-(4-nitro  
phenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine.

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To a stirred solution of 5-(2-cyanoethoxycarbonyl)-4-  
ethyl-1-{N-[3-(4-methoxycarbonyl-4-phenyl

piperidin-1-yl)propyl}carboxamido-6-(4-nitrophenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine (4.40 g, 6.8 mmol) in acetone (50 mL) at 0 °C, sodium hydroxide solution (1 N, 27.2 mL, 4 eq.) was added drop wise and the stirring was continued until the disappearance of the starting material (1 hour). Most of the acetone from the mixture was evaporated under reduced pressure while keeping the temperature at 0 °C and the residue was adjusted to pH 7.0 by the addition of 1N hydrochloric acid. The white precipitate of (+)-4-ethyl-1-{N-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]}carboxamido-6-(4-nitrophenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine-5-carboxylic acid formed was filtered and dried under vacuum (3.59 g, 89%). <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 1.07 (t, J = 7.5 Hz, 3 H), 1.55-1.70 (m, 2 H), 1.72-1.84 (m, 2 H), 1.84-2.15 (m, 2 H), 2.20-2.40 (m, 4 H), 2.70-2.90 (m, 2 H), 3.10-3.40 (m, 4 H), 3.51 (s, 3 H), 6.54 (s, 1 H), 7.18-7.38 (m, 6 H), 7.41 (d, J = 7.8 Hz, 2 H), 8.15 (d, J = 7.8 Hz, 2 H), 8.79 (br t, 1 H, NH), 10.05 (br s, 1 H, COOH); This product was used in the next step without any additional analysis.

A mixture of (+)-4-ethyl-1-{N-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]}carboxamido-6-(4-nitrophenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine-5-carboxylic acid (0.350 g, 0.59 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.2264 g, 1.181 mmol, 2eq.), and 4-(N,N-dimethylamino)pyridine (0.1443 g, 1.181 mmol, 2 eq) in anhydrous dichloromethane was stirred at room temperature for 2 h. To this, 40% aqueous ammonia (0.6 mL) was added and the stirring was continued for 12 h. The mixture was diluted with 100 mL of dichloromethane and washed with saturated aqueous ammonium chloride solution (3 X 20 mL). Solvent was evaporated from the dried (magnesium sulfate) dichloromethane solution and the residue was purified by column chromatography on silica gel using

chloroform-methanol-2M ammonia in methanol (500/16/8) as the eluent, to obtain the desired product as a white powder (0.24 g, 69%); m.p. 107-109 °C; <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 1.20 (t, J = 7.5 Hz, 3 H), 1.66-1.72 (m, 2 H), 1.79-2.00 (m, 3 H), 2.00-2.20 (m, 2 H), 2.29-2.35 (m, 2 H), 2.42-2.60 (m, 2 H), 2.62-2.82 (m, 3 H), 3.20-3.40 (m, 2 H), 3.60 (s, 3 H), 5.70 (br m, 2 H, NH<sub>2</sub>), 6.59 (s, 1 H), 7.20-7.39 (m, 6 H), 7.52 (d, J = 7.8 Hz, 2 H), 8.13 (d, J = 7.8 Hz, 2 H), 8.82 (t, 1 H); [α]<sub>D</sub> = +115.71 (c = 1.4, CHCl<sub>3</sub>); Anal. Calcd. for C<sub>30</sub>H<sub>36</sub>N<sub>6</sub>O<sub>7</sub>·0.8 H<sub>2</sub>O: C, 59.36; H, 6.24; N, 13.84. Found: C, 59.47; H, 6.07; N, 13.64.

#### Example 14

(+)-5-Carboxamido-6-(3,4-difluorophenyl)-4-ethyl-1-{N-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]}carboxamido-2-oxo-1,2,3,6-tetrahydropyrimidine (Scheme 5).

a. **Benzyl 3-[(3,4-difluorophenyl)methylene]-4-oxopentanoate.** A solution of benzyl propionylacetate (36.3 g, 176 mmol), 3,4-difluorobenzaldehyde (25.0 g, 176 mmol), piperidine (0.86 mL, 9.0 mmol) and acetic acid (0.49 mL, 9.0 mmol) were refluxed with removal of water using Dean-Stark apparatus for 5h. The solvent was removed in vacuo and the residue was dissolved in EtOAc. It was washed with water (100 mL) followed by brine (100 mL) and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Solvent was evaporated to get pale yellow syrup (60.2 g). It was used in the next step without further purification.

b. **5-(Benzyloxycarbonyl)-1,6-dihydro-2-methoxy-4-ethyl-6-(3,4-difluorophenyl)pyrimidine.** A suspension of benzyl 3-[(3,4-difluorophenyl)methylene]-4-oxopentanoate (16.0 g, 48.0 mmol), O-methylisourea hydrogen sulfate (16.65 g, 97.02 mmol), NaHCO<sub>3</sub> (16.3 g, 130.2 mmol) in DMF (190 mL) was stirred at 70°C for 20h.

After cooling to room temperature, the mixture was filtered and the filtrate was diluted with EtOAc (300 mL) and then washed with water (4X100 mL), brine (200 mL) and dried over Na<sub>2</sub>SO<sub>4</sub>. After removal of solvent, the residue was purified by column chromatography (SiO<sub>2</sub>, EtOAc/Hexane, 10%-30%) to get 5-(benzyloxycarbonyl)-1,6-dihydro-2-methoxy-4-methyl-6-(3,4-difluorophenyl)pyrimidine as a colorless oil (10.6 g, 58%). The NMR analysis showed it to be a mixture of amine/imine tautomers and was used as is in the next step.

**c. 5-(Benzyloxycarbonyl)-4-ethyl-1,6-dihydro-2-methoxy-6-(3,4-difluorophenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine.** To a well stirred solution of 5-(benzyloxy carbonyl)-1,6-dihydro-2-methoxy-4-ethyl-6-(3,4-difluorophenyl)pyrimidine (17.0 g, 44.04 mmol) and 4-dimethyl aminopyridine (6.99 g, 57.25 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (200 mL) was added a powder of 4-nitrophenyl chloroformate (11.54 g, 57.25 mmol) at room temperature. The reaction mixture was stirred for 12 hours and then the solvent was removed in vacuo. The residue was purified by chromatography (SiO<sub>2</sub>, EtOAc/Hexane 10-30%) to get 5-(benzyloxycarbonyl)-4-ethyl-1,6-dihydro-2-methoxy-6-(3,4-difluorophenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine as a colorless viscous oil (12.6 g, 50%). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.24 (t, J=7.2 Hz, 3H), 2.81-2.98 (m, 3H), 3.97 (s, 3H), 5.14 (AB<sub>q</sub>, δ<sub>A</sub>=5.08, δ<sub>B</sub>= 5.20, J= 12.3 Hz, 2H), 6.28 (s, 3H), 7.03-7.29 (m, 8H), 7.35 (d, J=9.2 Hz, 2H), 8.26 (d, J=9.2 Hz, 2H).

**d. 5-(Benzyloxycarbonyl)-4-ethyl-1,6-dihydro-1-{N-[2-phenyl)ethyl]}carboxamido-2-methoxy-6-(3,4-difluorophenyl)pyrimidine.** To a stirred mixture of 5-(benzyloxycarbonyl)-4-ethyl-1,6-dihydro-2-methoxy-6-(3,4-difluorophenyl)-1-[(4-nitrophenyloxy)carbonyl]



- pyrimidine (12.6 g, 22.86 mmol) in THF (150 mL) was added a solution of R-(+)- $\alpha$ -methyl benzylamine (3.53 mL, 27.44 mmol) at room temperature. The stirring was continued for 12 hours. Solvent was removed in vacuo.
- 5 The yellow residue was dissolved in chloroform (200 mL) and was washed with 10%  $K_2CO_3$  solution (2x30 mL). The organic layer was dried over  $Na_2SO_4$ , filtered and solvent was removed in vacuo. The resulting mixture of
- 10 diastereomers was separated by column chromatography over silica gel with 9:1 Pet. ether:Ether to 4:1 Pet. ether:Ether. First major product to elute was (+)-5-(benzyloxycarbonyl)-4-ethyl-1,6-dihydro-1-{N-[2-phenyl)ethyl]}carboxamido-2-methoxy-6-(3,4-difluorophenyl)pyrimidine. Colorless oil,  $R_f$  = 0.31(4:1
- 15 Pet ether:ether), wt. = 3.8 g (60%),  $[\alpha]_D = +267.05$  (c = 0.76,  $CHCl_3$ )  $^1H$  NMR:  $\delta$  1.22 (t, J=7.5 Hz, 3H), 1.52 (d, J=6.9 Hz, 3H), 2.88 (q, J=6.0 Hz, 2H), 3.99 (s, 3H), 4.99 (m, 1H), 5.09 (AB<sub>q</sub>,  $\delta_A$ =5.00,  $\delta_B$ = 5.19, J= 12.6 Hz, 2H), 6.66 (s, 1H), 6.99-7.36 (m, 13H).; Second major
- 20 product to elute was (-)-5-(benzyloxycarbonyl)-4-ethyl-1,6-dihydro-1-{N-[2-phenyl)ethyl]}carboxamido-2-methoxy-6-(3,4-difluorophenyl)pyrimidine. Colorless oil.  $R_f$  = 0.22(4:1 Pet ether:ether), wt. = 3.2 g (51.2%),  $[\alpha]_D$
- 25 = -146.89 (c = 0.38,  $CHCl_3$ ),  $^1H$  NMR:  $\delta$  1.22 (t, J=7.2 Hz, 3H), 1.49 (d, J=6.6 Hz, 3H), 2.88 (q, J=6.0 Hz, 2H), 3.94 (s, 3H), 5.03 (m, 1H), 5.11 (AB<sub>q</sub>,  $\delta_A$ =5.02,  $\delta_B$ = 5.19, J= 12.6 Hz, 2H), 6.68 (s, 1H), 6.91-7.34 (m, 13H).
- 30 e. (+)-5-(Benzyloxycarbonyl)-1,6-dihydro-2-methoxy-4-ethyl-6-(3,4-difluorophenyl)pyrimidine. To a stirred solution of (+)-5-(benzyloxycarbonyl)-4-ethyl-1,6-dihydro-1-{N-[2-phenyl)ethyl]}carboxamido-2-methoxy-6-(3,4-difluorophenyl)pyrimidine (1.83 mmol, 1.0 g) in
- 35 toluene (10 mL) was added 1,8-diazabicyclo[5,4,0]-undec-7-ene (0.81 mmol, 0.12 mL) at room temperature and the resulting solution was heated to reflux for 5h and

then stirred for 12h at room temperature. The solvent was evaporated and the residue was purified by flash column chromatography on silica gel with 3:1 EtOAc/Hexanes as the eluting system. 0.56 g of the (+)-  
5 5-(benzyloxycarbonyl)-1,6-dihydro-2-methoxy-4-ethyl-6-(3,4-difluorophenyl)pyrimidine was obtained (77%).

f. (+)-5-(Benzyloxycarbonyl)-4-ethyl-1,6-dihydro-2-methoxy-6-(3,4-difluorophenyl)-1-[(4-nitrophenyloxy)  
10 carbonyl]pyrimidine. To a well stirred solution of (+)-5-(benzyloxycarbonyl)-1,6-dihydro-2-methoxy-4-ethyl-6-(3,4-difluorophenyl)pyrimidine (17.0 g, 44.04 mmol) and 4-dimethylaminopyridine (6.99 g, 57.25 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (200 mL) was added a powder of 4-nitrophenyl  
15 chloroformate 11.54 g, 57.25 mmol) at room temperature. The reaction mixture was stirred for 12 hours and then the solvent was removed in vacuo. The residue was purified by chromatography (SiO<sub>2</sub>, EtOAc/Hexane 10-30%) to get (+)-5-(benzyloxycarbonyl)-4-ethyl-1,6-dihydro-2-  
20 methoxy-6-(3,4-difluorophenyl)-1-[(4-nitrophenyloxy) carbonyl]pyrimidine as a colorless viscous oil (19.3 g, 76%).

g. (+)-5-(Benzyloxycarbonyl)-6-(3,4-difluorophenyl)-4-ethyl-1-{N-[3-(4-methoxycarbonyl-4-phenyl  
25 piperidin-1-yl)propyl]}carboxamido-2-oxo-1,2,3,6-tetrahydropyrimidine. To a stirred mixture of (+)-5-(benzyloxycarbonyl)-4-ethyl-1,6-dihydro-2-methoxy-6-(3,4-difluorophenyl)-1-[(4-nitrophenyloxy)  
30 carbonyl]pyrimidine (0.55 g, 1.12 mmol) in THF (5 mL) was added a solution of 3-[4-methoxycarbonyl-4-phenylpiperidin-1-yl]propylamine (0.31 g, 1.12 mmol) in THF (5 mL) at room temperature. The stirring was continued for 12 hours. A solution of 10% HCl in water  
35 (2 mL) was added and stirred for 2 h. The solvent was then removed in vacuo and the residue was extracted with ethyl acetate (3 X 10 mL). It was washed with 10%

aq. KOH solution, dried over  $\text{Na}_2\text{SO}_4$  and solvent was removed in vacuo to obtain (+)-5-(benzyloxycarbonyl)-6-(3,4-difluorophenyl)-4-ethyl-1-{N-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]}carboxamido-2-oxo-1,2,3,6-tetrahydropyrimidine as a white foamy compound (0.73 g, 96.6%) the purity of which was characterized as its HCl salt. It was used in the next step without further purification. Anal. Calcd. for  $\text{C}_{37}\text{H}_{41}\text{ClF}_2\text{N}_4\text{O}_6 \cdot 0.5\text{CHCl}_3$ : C, 58.43; H, 5.43; N, 7.27. Found: C, 58.11, H; 5.85; N, 7.64.

**h. 6-(3,4-Difluorophenyl)-4-ethyl-1-{N-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]}carboxamido-1,2,3,6-tetrahydro-2-oxopyrimidine-5-carboxylic acid.** To a suspension of 10% Pd-C (0.14 g, 20% by wt.) in MeOH (3 mL) was added the solution of (+)-5-(benzyloxycarbonyl)-6-(3,4-difluorophenyl)-4-ethyl-1-{N-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]}carboxamido-2-oxo-1,2,3,6-tetrahydropyrimidine at room temperature with constant stirring. A balloon filled with  $\text{H}_2$  was attached and the reaction mixture was stirred for 48 hours. The black suspension was filtered through a pad of celite and the filtrate was concentrated in vacuo. The residue was purified by column chromatography ( $\text{SiO}_2$ , 10% MeOH in EtOAc) to obtain (+)-6-(3,4-difluorophenyl)-4-ethyl-1-{N-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]}carboxamido-1,2,3,6-tetrahydro-2-oxopyrimidine-5-carboxylic acid as a white solid. M.P. 184-186 °C;  $[\alpha]_D = +142.2$  ( $c = 0.25$ ,  $\text{CHCl}_3$ ) The purity was checked by combustion analysis as a HCl salt. Anal. Calcd. for  $\text{C}_{30}\text{H}_{35}\text{ClF}_2\text{N}_4\text{O}_6 \cdot 0.3\text{CHCl}_3$ : C, 55.40; H, 5.42; N, 8.53. Found: C, 55.34; H; 5.80; N, 8.13.

**i. (+)-5-Carboxamido-6-(3,4-difluorophenyl)-4-ethyl-1-{N-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]}carboxamido-2-oxo-1,2,3,6-tetrahydro**

**pyrimidine.**

To a solution of (+)-6-(3,4-difluorophenyl)-4-ethyl-1-{N-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]}carboxamido-1,2,3,6-tetrahydro-2-oxopyrimidine-5-carboxylic acid (0.22 g, 0.375 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (3 mL) was added 4-N,N-dimethylamino pyridine (0.14 g, 1.12 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.21 g, 1.12 mmol) under argon and the resulting solution was stirred at room temperature for 2h. Three drops of saturated NH<sub>4</sub>OH was then added and the solution was stirred for 48 h. The solution was washed with water (5 ml) and dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed in vacuo and the residue was purified by column chromatography (SiO<sub>2</sub>, 10% MeOH in CHCl<sub>3</sub>) to obtain 5-carboxamido-6-(3,4-difluorophenyl)-4-ethyl-1-{N-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]}carboxamido-2-oxo-1,2,3,6-tetrahydropyrimidine as a beige solid (0.1 g, 45%). Characterized as HCl salt. M.P. 136-138°C., [α]<sub>D</sub> = +111.44 (c = 0.18, MeOH): δ 1.21 (t, J=7.5 Hz, 3H), 1.60-1.75 (m, 2H), 1.92-2.1 (m, 8H), 2.33 (t, J=6.6 Hz, 2H), 2.44-2.52 (m, 2H), 2.53-2.84 (m, 4H), 3.27-3.32 (m, 2H), 3.60 (s, 3H), 5.60 (br s, 2H), 6.47 (s, 1H), 7.05-7.33 (m, 8H), 8.80 (br t, 1H), Anal. Calcd. for C<sub>30</sub>H<sub>35</sub>ClF<sub>2</sub>N<sub>4</sub>O<sub>6</sub>·1.0 CHCl<sub>3</sub>:C, 50.35; H, 5.04; N, 9.47. Found: C, 50.40; H, 5.33; N, 9.13.

**Example 15**

**6-(3,4-Difluorophenyl)-5-methoxycarbonyl-4-methyl-2-oxo-1-{N-[4-(2-pyridyl)-piperidine-1-yl]propyl}carboxamido-1,2,3,6-tetrahydropyrimidine dihydrochloride (Scheme 7).**

**a. 1-Benzyl-4-cyano-4-(2-pyridyl)piperidine.** To a mixture of N,N-bis-(2-chloroethyl)benzylamine (E.Szarvasi, Eur. J. Med. Chem. Chim. Ther. 11(2), 115-124, 1976) (60 g, 22 mmol), 2-pyridylacetonitrile (2.51

ml, 22 mmol) and tetrabutylammonium hydrogen sulfate (0.26 g, 0.7 mmol) in toluene (10 ml), sodium hydroxide solution (2.43 g in 4.86 ml H<sub>2</sub>O) was added over a 20 minute period. The reaction mixture was heated at 65 °C for 4 hours. The reaction mixture was cooled to room temperature, 10 ml of water was added and the solution partitioned between ethyl acetate (45 ml) and water. The organic layer was dried over sodium sulfate, filtered and concentrated. Purification of the crude product by column chromatography (hexane:EtOAc, 2:3) gave 6.2 g (87%) of the title compound as a red solid; <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 2.05 (d, J = 13.1 Hz, 2 H), 2.30 (t, J = 13.2 Hz, 2 H), 2.48 (t, J = 13.2 Hz, 2 H), 2.97 (d, J = 12.1 Hz, 2 H), 3.57 (s, 2 H), 7.19-7.27 (m, 6 H), 7.30 (d, J = 7.6 Hz, 1 H), 7.60 (t, J = 7.6 Hz, 1 H), 8.58 (d, J = 4.6 Hz, 1H).

**b. 1-Benzyl-4-carboxamido-4-(2-pyridyl)piperidine.** To 1-benzyl-4-cyano-4-(2-pyridyl)piperidine (4.5 g, 14.3 mmol), 10 ml of conc.H<sub>2</sub>SO<sub>4</sub> was added and the solution was stirred at room temperature for 24 hours. It was cooled to 0 °C, diluted with ice pieces and poured into crushed ice. The mixture was then carefully neutralized with 50 % NaOH solution. The reaction mixture was repeatedly extracted with chloroform (3 x 25 ml), dried over sodium sulfate, filtered and concentrated to give 4.5 g (95%) of the crude product which was used as such for the subsequent step; <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 2.21-2.28 (m, 2 H), 2.47 (s, 6 H), 3.41 (s, 2 H), 5.23 (s, 1 H), 6.40 (s, 1 H), 7.12-7.29 (m, 6 H), 7.33 (d, J = 7.6 Hz, 1 H), 7.63 (t, J = 7.6 Hz, 1 H), 8.55 (d, J = 4.6 Hz, 1 H).

**c. 1-Benzyl-4-(2-pyridyl)-piperidine.** To 1-benzyl-4-carboxamido-4-(2-pyridyl)piperidine (4.5 g, 13.5 mmol) in anhydrous methanol (100 ml), HCl gas was bubbled through the solution at 0 °C for 15 minutes. The

reaction mixture was then refluxed for 24 hours. It was cooled to room temperature, concentrated, neutralized with 50 % NaOH and repeatedly extracted with chloroform (3 x 25 ml). The combined organic layer was then dried over sodium sulfate, filtered and concentrated. Flash chromatography (hexane:ethylacetate, 1:4) of the crude product yielded 1.72 g (50%) of the product as a syrup; <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 1.8-1.94 (m, 4 H), 2.11 (t, J = 11.4 Hz, 2 H), 2.70-2.72 (m, 1 H), 3.02 (d, J = 11.4 Hz, 2 H), 3.54 (s, 2 H), 7.07-7.36 (m, 7 H), 7.58 (t, J = 7.6 Hz, 1 H), 8.52 (d, J = 4.6 Hz, 1 H).

**d. 3-[4-(2-Pyridyl)-piperidine-1-yl]propylamine (Scheme 6).** To 1-Benzyl-4-(2-pyridyl)-piperidine (3.26 g, 12.9 mmol) in dry methanol (25 ml), 10% palladium hydroxide (1.9 g) was added and the solution was hydrogenated at 200 psi for 24 hours. The solution was filtered over celite, concentrated to give 2.1 g (99%) of 4-(2-pyridyl)-piperidine which was used as such for the subsequent step. A mixture of 3-bromopropylamine hydrobromide (20 g, 91.3 mmol), potassium carbonate (37.85 g, 273.9 mmol) and di-tert-butylidicarbonate (21.90 g, 100 mmol) in methanol was stirred at room temperature for 24 hours. The reaction mixture was concentrated and partitioned between 250 ml EtOAc and 50 ml water, dried over sodium sulfate, filtered and concentrated. Purification of the crude product by column chromatography (Hexane: EtOAc, 4.5:0.5) gave 17.5 g (80%) of the product as a pale yellow oil. To a stirred solution of the 4-(2-pyridyl)-piperidine (1.86 g, 11.4 mmol) in dioxane ( 20 ml), N-(tert-butoxycarbonyl)-3-bromopropylamine (2.82 g, 11.4 mmol) and potassium carbonate (3.16 g, 22.9 mmol) were added and the solution refluxed for 24 hours. The reaction mixture was cooled to room temperature, concentrated and partitioned between 40 ml chloroform and 5 ml

water. The organic layer was dried over sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (ethyl acetate: methanol, 4:1) to yield 1.86 g (49 %) of the required product as a colorless oil; <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 1.45 (s, 9 H), 1.54-1.69 (m, 8 H), 2.21-2.68 (m, 2 H), 2.74-2.80 (m, 1 H), 3.02-3.22 (m, 4 H), 5.41 (s, 1H), 7.13-7.17 (m, 1 H), 7.33 (d, *J* = 7.93 Hz, 1 H), 7.63 (t, *J* = 7.6 Hz, 1 H), 8.54 (d, *J* = 4.6 Hz, 1 H). To N-(tert-butoxycarbonyl)-3-[4-(2-pyridyl)-piperidin-1-yl]propylamine (0.15g, 0.45 mmol) in 5 ml of dichloromethane, 1 ml of trifluoroacetic acid was added and the solution stirred at room temperature for 1 hour. The solution was concentrated, neutralized with 10 % KOH solution and extracted into 25 ml of dichloromethane. The organic layer was dried over sodium sulfate, filtered and concentrated to give 0.098 g (100%) of 3-[4-(2-pyridyl)-piperidin-1-yl]propylamine which was used as such for the subsequent step (step h).

**e. Methyl 2-{(3,4-difluorophenyl)methylene}-3-oxobutyrates.** A mixture of 3,4-difluorobenzaldehyde (14.2 g, 0.1 mol), methyl acetoacetate (12.2 g, 0.105 mol), piperidine (0.430 g, 5 mmol), and acetic acid (0.30 g, 5 mmol) in benzene (150 mL) was stirred and refluxed with a Dean-Stark trap for 8 hours. Benzene was evaporated, the residue was dissolved in ethyl acetate (200 mL) and washed with brine (50 mL), saturated potassium bisulfate solution (50 mL), and saturated sodium bicarbonate solution in sequence. The ethyl acetate solution was dried (magnesium sulfate), solvent removed under reduced pressure and the residue was purified by column chromatography (SiO<sub>2</sub>, EtOAc/hexane, 10%-15%). The product, methyl 2-{(3,4-difluorophenyl)methylene}-3-oxobutyrates, was obtained as a yellow oil (0.98 g, 98.3%) and was used in the

next step without any further characterization.

5 f. 6-(3,4-Difluorophenyl)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methylpyrimidine. A mixture of methyl 2-[(3,4-difluorophenyl)methylene]-3-oxobutyr-  
10 ate (8.8 g, 36.6 mmol), O-methylisourea hydrogen sulfate (9.4 g, 55 mmol), and NaHCO<sub>3</sub> (12.3 g, 0.146 mol) in DMF (30 mL) was stirred and heated at 70 °C for 16 hours. The mixture was cooled, diluted with EtOAc (300 mL) and  
15 washed with water (5 X 300 mL), brine (300 mL), and dried (MgSO<sub>4</sub>). Solvent was evaporated and the crude product was purified by flash column chromatography on silica gel using 10% through 20% EtOAc in hexane as the gradient eluent, to leave the product as an oil (3.82 g, 30.2%); <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 2.32, 2.39 (2 s, 3 H), 3.58, 3.64 (2 s, 3 H), 3.72, 3.85 (2 s, 3 H), 5.55 (s, 1 H), 6.13-7.8 (m, 4 H).

20 g. 6-(3,4-Difluorophenyl)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-1-[(4-nitrophenoxy)carbonyl]pyrimidine.

To a solution of 6-(3,4-difluorophenyl)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methylpyrimidine (2.82 g, 9.52 mmol) and 4-dimethylaminopyridine (1.16 g, 9.52  
25 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (50 mL), at 0-5 °C, 4-nitrophenyl chloroformate (1.82 g, 9.04 mmol) was added and the mixture was allowed to warm to room temperature. After 12 hours solvent was evaporated and the residue was purified by flash column chromatography (SiO<sub>2</sub>,  
30 EtOAc/hexane, 10%-15%) to obtain the product as white crystals (3.72, 84.7%); m.p. 172-174 °C; <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 2.51 (s, 3 H), 3.72 (s, 3 H), 3.97 (s, 3 H), 6.26 (s, 1 H), 7.0-7.3 (m, 3 H), 7.38 (d, J = 9.3 Hz, 2 H), 8.32 (d, J = 9.3 Hz, 2 H).

35

h. 6-(3,4-Difluorophenyl)-5-methoxycarbonyl-4-methyl-2-oxo-1-[N-[4-(2-pyridyl)-piperidine-1-yl]propyl]



**carboxamido-1,2,3,6-tetrahydropyrimidine dihydrochloride.** To 6-(3,4-difluorophenyl)-1,6-

- 5 10 ml of dry dichloromethane, 3-[4-(2-pyridyl)-piperidine-1-yl]propylamine (0.038 g, 0.17 mmol) was added and the solution was stirred at room temperature for 24 hours. The reaction mixture was stirred for another 1 hour after addition of 2 ml of 6N HCl. After  
10 neutralization with 10% aqueous KOH solution, the reaction mixture was extracted into dichloromethane (3 x 10 ml). The organic layer was dried over sodium sulfate, filtered and concentrated. The crude product was purified by flash chromatography ( EtOAc: MeOH,  
15 4.5:0.5) to give 0.040 g (89%) as a syrup ; <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 1.73-2.11 (m, 7 H), 2.41 (s, 6 H), 2.69 (m, 1 H), 3.04 (d, J = 12.1 Hz, 2 H) , 3.31-3.48 (m, 2 H), 3.71 ( s, 3 H), 6.70 (s, 1 H), 7.24-7.27 (m, 5 H), 7.61 ( t, J = 8.0 Hz, 2 H), 8.51 (d, J = 4.6 Hz, 1 H), 8.89  
20 (t, J = 5.1 Hz, 2 H).

- To the free base (0.04g, 0.07 mmol) in 4 ml of dichloromethane, 5 ml of 1N HCl in ether was added, and the solution concentrated under reduced pressure.  
25 Recrystallization from ether gave 0.046 g (98%) of 6-(3,4-difluorophenyl)-5-methoxycarbonyl-4-methyl-2-oxo-1-{N-[4-(2-pyridyl)-piperidine-1-yl]propyl}carboxamido-1,2,3,6-tetrahydropyrimidine dihydrochloride as a white solid; m.p. 170-174 °C; Anal. Calcd. for  
30 C<sub>27</sub>H<sub>33</sub>Cl<sub>2</sub>F<sub>2</sub>N<sub>5</sub>O<sub>4</sub>.1.0 H<sub>2</sub>O: C, 52.43; H, 5.70, N 11.30. Found: C, 52.16; H 5.35; N 11.10.

#### Example 16

- 6-(3,4-Benzofurazan-5-yl)-5-methoxycarbonyl-4-methyl-2-oxo-1-{N-[4-(2-pyridyl)-piperidin-1-yl]propyl}carbox  
35 amido-1,2,3,6-tetrahydropyrimidine dihydrochloride (Scheme 8).

**5-Methylbenzfuroxan.** 4-Methyl-2-nitroaniline (100 g, 0.650 mol) was suspended in saturated alcoholic sodium hydroxide solution (1.50 l). To this suspension was added with cooling (5 °C) commercial aqueous sodium hypochlorite till the red color disappeared. The fluffy yellow precipitate formed was filtered, washed with cold water and recrystallized from ethanol to get 5-Methylbenzfuroxan (88.2 g, 89 % yield) as a pale solid.

**5-Methylbenzofurazan.** To 5-Methylbenzfuroxan (88.2 g, 0.59. mol) in refluxing EtOH (75 ml) was added dropwise P(OEt)<sub>3</sub> (150 ml). When addition was complete, refluxing was continued for 1 more hour. The solvent was removed by rotary evaporation and the residue shaken with water (200 mL) and allowed to stand overnight at (0-5 °C). The brown solid so obtained was filtered, washed with water and chromatographed on silica gel to yield 5-Methylbenzofurazan (70 g, 87 %) as white needle.

**5-Dibromomethylbenzofurazan.** 5-Methylbenzofurazan (70 g, 0.52 mol), NBS (325 g), and benzoyl peroxide (0.5 g) were refluxed with stirring in carbon tetrachloride (1.5 L) with exclusion of moisture for 30 hours. The reaction mixture was washed with water (2X0.5L), dried (NaSO<sub>4</sub>), and the solvent was removed in vacuo. The residue was chromatographed (silica, EtOAc-hexane, 1:150) to give 122 g (80%) of the title compound. The resulting white solid was used in the next step without any further characterization.

**5-Formylbenzofurazan.** To a refluxing mixture of the dibromomethylbenzofurazan (122 g, 418 mmol) in EtOH (1 L) was added AgNO<sub>3</sub> (163 g) in 2 L of water. Refluxing was continued for 2 hours. The mixture was cooled and the AgBr was removed by filtration through Celite, and

the solvent was concentrated to a small volume. The resulting solution was extracted with toluene (10 X 100 mL), dried (MgSO<sub>4</sub>), and the solvent was removed in vacuo. The residue was chromatographed on silica (EtOAc-hexane, 8:1000) to give 48.2 g of the title aldehyde (78%) as a white solid.

**a. Methyl 2-{(benzofuran-5-yl)methylene}-3-oxobutyrates.**

10 A mixture of 5-Formylbenzofurazan (0.6 g, 4.1 mmol), methyl acetoacetate (0.52 g, 4.5 mmol), piperidine (0.019 g, 0.225 mmol), and acetic acid (0.014 g, 0.225 mmol) in benzene (30 mL) was stirred and refluxed with a Dean-Stark trap for 8 h. Benzene was evaporated, the  
15 residue was dissolved in ethyl acetate (80 mL) and washed with brine (50 mL), saturated potassium bisulfate solution (50 mL), and saturated sodium bicarbonate solution in sequence. The ethyl acetate solution was dried (magnesium sulfate), solvent removed  
20 under reduced pressure and the residue was purified by column chromatography (SiO<sub>2</sub>, EtOAc/hexane, 10%-15%). The product, methyl 2-{(benzofuran-5-yl)methylene}-3-oxobutyrates, was obtained as an oil (0.98 g, 98.3%) and was used in the next step without any further  
25 characterization.

**b. 6-(Benzofurazan-5-yl)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methylpyrimidine.** A mixture of methyl 2-{(benzofuran-5-yl)methylene}-3-oxobutyrates  
30 (1.02 g, 4.1 mmol), O-methylisourea hydrogen sulfate (1.06 g, 6.2 mmol), and NaHCO<sub>3</sub> (1.3 g, 16.4 mmol) in DMF (15 mL) was stirred and heated at 70 °C for 16 h. The mixture was cooled, diluted with EtOAc (50 mL) and washed with water (5X 50 mL), brine (50 mL), and dried  
35 (MgSO<sub>4</sub>). Solvent was evaporated and the crude product was purified by flash column chromatography on silica gel using 10% through 20% EtOAc in hexane as the

gradient eluent, to leave the product as an oil (0.52 g, 43%); <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 2.38, 2.42 (2 s, 3 H), 3.60, 3.66 (2 s, 3 H), 3.74, 3.82 (2 s, 3 H), 5.53, 5.68 (2 s, 1 H), 6.31, 6.32 (br s, 1 H), 7.0-7.8 (m, 3 H).

5

**c. 6-(Benzofurazan-5-yl)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-1-[(4-nitrophenoxy)carbonyl]pyrimidine.**

To a solution of 6-(benzofuran-5-yl)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methylpyrimidine (0.485 g, 1.6 mmol) and 4-dimethylaminopyridine (0.2 g, 1.6 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL), at 0-5 °C, was added 4-nitrophenyl chloroformate (0.307 g, 1.52 mmol) and the mixture was allowed to warm to room temperature. After 12 hours solvent was evaporated and the residue was purified by flash column chromatography (SiO<sub>2</sub>, EtOAc/hexane, 10%-15%) to obtain the product as white crystals (0.665 g, 89%); m.p. 180-183 °C; <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 2.54 (s, 3 H), 3.75 (s, 3 H), 3.98 (s, 3 H), 6.37 (s, 1 H), 7.40 (d, J = 9.3 Hz, 2 H), 7.52 (d, J = 9.0 Hz, 1 H), 7.68 (s, 1 H), 7.84 (d, J = 9.0 Hz, 1 H), 8.32 (d, J = 9.3 Hz, 2 H).

**d. 6-(3,4-Benzofurazan-5-yl)-5-methoxycarbonyl-4-methyl-2-oxo-1-[N-[4-(2-pyridyl)-piperidin-1-yl]propyl]carboxamido-1,2,3,6-tetrahydropyrimidine dihydrochloride.** To 6-(benzofurazan-5-yl)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-1-(4-nitrophenoxy)carbonylpyrimidine (0.04 g, 0.085 mmol) in 10 ml of dry dichloromethane, 3-[4-(2-pyridyl)-piperidine-1-yl]propylamine (0.037 g, 0.17 mmol) was added and the solution was stirred at room temperature for 24 hours. The reaction mixture was stirred for another 1 hour after addition of 2 ml of 6N HCl. After neutralization with 10% aqueous KOH solution, the reaction mixture was extracted into dichloromethane (3 x 10 ml). The organic layer was dried over sodium

sulfate, filtered and concentrated. The crude product was purified by flash chromatography ( EtOAc: MeOH, 4.5:0.5) to give 0.040 g (89%) as a syrup ; <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 1.74-2.10 (m, 7 H), 2.46 (s, 6 H), 2.70-2.72 (m, 1 H), 3.05 (d, J = 12.1 Hz, 2 H), 3.34-3.48 (m, 2 H), 3.76 ( s, 3 H), 6.82 (s, 1 H), 7.11-7.32 (m, 3 H), 7.54-7.78 (m, 4 H), 8.53 (d, J = 4.6 Hz, 1 H), 8.89 (t, J = 5.16 Hz, 2 H).

To the free base ( 0.04g, 0.07 mmol)in 4 ml of dichloromethane, 5 ml of 1N HCl in ether was added, and the solution concentrated under reduced pressure. Recrystallization from ether gave 0.040 g (87%) of 6-(3,4-benzofurazan-5-yl)-5-methoxycarbonyl-4-methyl-2-oxo-1-{N-[4-(2-pyridyl)-piperidine-1-yl]propyl} carboxamido-1,2,3,6-tetrahydropyrimidine dihydrochloride as a white solid; m.p. 200-204 °C; Anal. Calcd. for C<sub>27</sub>H<sub>33</sub>Cl<sub>2</sub>N<sub>7</sub>O<sub>5</sub>·2.5 H<sub>2</sub>O: C, 49.77; H,5.88. Found: C, 49.41; H 5.20.

#### Example 17

6-(3,4-Difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-1-(5-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)-pentyl)-2,4-dimethylpyrimidine (Scheme 9).

a. 6-(3,4-Difluorophenyl)-1,6-dihydro-2,4-dimethyl-5-methoxycarbonylpyrimidine. To a solution of acetamidine hydrochloride (1.53 g, 16.2 mmol.) in DMF (10 mL) were added a solution of potassium tert-butoxide (1.33 g, 11.8 mmol.) in DMF (10 mL) and a solution of methyl {2-(3,4-difluorophenyl) methylene}-3-oxobutanoate (2.6 g, 10.8 mmol.) in DMF (10 mL) at 0°C. After the mixture was stirred for 0.5 hour at 0°C, p-toluenesulfonic acid monohydrate (4.1 g, 21.5 mmol.) was added. The mixture was heated at 100-120°C for 2 hrs. The reaction mixture was cooled to room temperature, quenched with aqueous NaOH solution (2N,

60 mL), and extracted with ether. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated. The residue was flash chromatographed over silica gel (eluent: ethyl acetate) to give the product in 59% yield (1.8 g) as a yellow solid: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.98 (3H, s), 2.31 (3H, s), 3.59 (3H, s), 5.47 (1H, s), 7.03-7.05 (3H, m).

**b. 1-(5-Chloropentyl)-6-(3,4-difluorophenyl)-1,6-dihydro-2,4-dimethyl-5-methoxycarbonylpyrimidine.** To a suspension of NaH (90 mg, 60% dispersion in mineral oil, 2.25 mmol.) in THF (7 mL) was added a solution of the above yellow solid (0.6 g, 2.14 mmol.) in THF (8 mL) at 0°C. After 20 min, 1-bromo-5-chloropentane (1 mL, d 1.408, 7.59 mmol.) was added. The reaction mixture was then refluxed overnight. After the removal of the solvent, the residue was flash chromatographed over silica gel (eluent: ethyl acetate) to give the product in 75% yield (0.614 g) as a yellow oil: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.42-1.75 (6H, m), 2.17 (3H, s), 2.28 (3H, s), 3.05-3.45 (2H, m), 3.49 (2H, t, J=5.88Hz), 3.63 (3H, s), 5.23 (1H, s), 7.01-7.15 (3H, m).

**c. 6-(3,4-Difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-1-(5-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)-pentyl)-2,4-dimethylpyrimidine.** A mixture of the above yellow oil (0.667 g, 1.73 mmol.), 4-methoxycarbonyl-4-phenyl piperidine (0.76 g, 3.47 mmol.), potassium carbonate (0.96 g, 6.95 mmol.), sodium iodide (0.52 g, 3.47 mmol.) and 1,4-dioxane (15 mL) was refluxed overnight. The undissolved solid was then filtered off and the solvent was evaporated. The residue was flash chromatographed over silica gel (eluent: 80:20 v/v ethyl acetate-2M ammonia in methanol) to give the title compound in 78% yield (0.768 g) as a yellow oil: CIMS, m/z 568 (MH<sup>+</sup>); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.23-1.28 (2H, m), 1.43-1.51 (2H, m), 1.77-2.13 (8H, m), 2.16 (3H, s), 2.28 (3H, s), 2.47-

2.55 (2H, m), 2.74-2.81 (2H, m), 3.00-3.12 (1H, m), 3.22-3.38 (1H, m), 3.613 (3H, s), 3.615 (3H, s), 5.22 (1H, s), 6.99-7.35 (3H, m).

- 5 Treatment of the free base with 2 equivalents of 1M HCl in ether gave the HCl salt as a yellow foam: m.p. 170-176°C. Anal. Calc. for  $C_{32}H_{39}F_2N_5O_4 \cdot 2HCl \cdot 2.3H_2O$ : C, 56.35; H, 6.74; N, 6.16; Found: C, 56.34; H, 6.62; N, 5.86.

10 **Example 18**

(+)-6-(3,4-Difluorophenyl)-5-methoxycarbonyl-4-methyl-2-oxo-1-{N-[3-(4-(2-pyridyl)-4-hydroxypiperidin-1-yl)propyl]}carboxamido-1,2,3,6-tetrahydropyrimidine dihydrochloride.

- 15 A solution of (+)-6-(3,4-difluorophenyl)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-1-(4-nitrophenoxy)carbonylpyrimidine (0.894 g, 2 mmol), 3-[4-(2-pyridyl)-4-hydroxypiperidin-1-yl]propylamine (0.517 g, 2.2 mmol) in tetrahydrofuran (100 mL) was stirred at room  
20 temperature for 24 hours. The reaction mixture was stirred for another 1 hour after addition of 2 mL of 6N HCl. Solvent was evaporated at reduced pressure and the residue was basified by treatment with 10% aqueous KOH solution, extracted with dichloromethane (3 x 10  
25 mL). The combined extracts were dried over potassium carbonate, and solvent evaporated. The crude product was purified by flash chromatography on silica gel (dichloromethane:MeOH:2M ammonia in MeOH, 90:8:4) to give 1.20 g (97%) as a syrup. The free base was  
30 dissolved in 20 mL anhydrous ether, cooled to 0-5 °C and treated with 10 mL of 1N HCl in ether. The white powder was filtered and dried to give 6-(3,4-difluorophenyl)-5-methoxycarbonyl-4-methyl-2-oxo-1-{N-[3-(4-(2-pyridyl)-4-hydroxypiperidin-1-yl)propyl]}carboxamido-  
35 1,2,3,6-tetrahydropyrimidine dihydrochloride; m.p. 200-206 °C;  $[\alpha]_D = +91$  (c = 1.15 g, in 100 mL of chloroform). Anal. Calcd. for  $C_{27}H_{33}Cl_2F_2N_5O_4 \cdot 0.4CHCl_3$ : C,

48.18; H, 4.92; N, 10.18. Found: C, 48.34; H, 5.01; N, 10.08.

**Example 19**

5     **(+)-1,2,3,6-Tetrahydro-1-{N-[4-(2-pyridyl)-piperidin-1-yl]-(2-hydroxypropyl)}carboxamido-5-methoxycarbonyl-2-oxo-6-(3,4-difluorophenyl)-4-methylpyrimidine dihydrochloride**

10     **a) 3-[4-(2-Pyridyl)-piperidin-1-yl](2-hydroxypropyl) phthalimide**

A mixture of 4-(2-pyridyl)piperidine (3.25 g, 19.90 mmol) and 2,3-epoxypropylphthalimide (4.449 g, 21.89 mmol) in DMF (20 mL) was stirred and heated at 70 °C for 15 48 h. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel using chloroform-methanol-2M ammonia in methanol (1000/28/14) as the eluent, to obtain the desired product as a viscous oil (6.15 g, 20 84%).

**b) 3-[4-(2-Pyridyl)-piperidin-1-yl]-2-hydroxypropylamine**

A mixture of 3-[4-(2-pyridyl)-piperidin-1-yl](2-hydroxypropyl)phthalimide (1.35 g, 3.68 mmol) and 25 hydrazine (0.588 g, 18.4 mmol) in methanol (15 mL) was stirred and refluxed for 4.5 h. It was cooled, filtered, and the solid was washed with methanol (30 mL). Evaporation of solvent from the filtrate gave the 30 product as a viscous oil (0.85 g, 98%).

**c) (+)-1,2,3,6-Tetrahydro-1-{N-[4-(2-pyridyl)-piperidin-1-yl]-(2-hydroxypropyl)}carboxamido-5-methoxycarbonyl-2-oxo-6-(3,4-difluorophenyl)-4-methylpyrimidine dihydrochloride**

35     A solution of (+)-6-(3,4-difluorophenyl)-1,2,3,6-tetrahydro-2-oxo-5-methoxycarbonyl-4-methyl-1-(4-



nitrophenoxy) carbonylpyrimidine (105 mg, 0.23 mmol),  
3-[4-(2-pyridyl)piperidin-1-yl]-2-hydroxypropylamine  
(50 mg, 0.23 mmol) in tetrahydrofuran (20 mL) was  
stirred at room temperature for 24 hours. Solvent was  
5 evaporated at reduced pressure and the residue was  
basified by treatment with 10% aqueous KOH solution,  
extracted with dichloromethane (3 x 10 mL). The  
combined extracts were dried over potassium carbonate,  
and solvent evaporated. The crude product was purified  
10 by flash chromatography (dichloromethane:MeOH:2M  
ammonia in MeOH, 90:8:4) to give 120 mg (97%) as a  
syrup; The HCl salt was prepared by treatment with 1N  
HCl in ether; m.p. 215-220 °C;  $[\alpha]_D = +41$  (c = 1.15 g, in  
100 mL of methanol). Anal. Calcd. for  $C_{27}H_{33}N_5O_6F_2Cl_2 \cdot 0.8$   
15 MeOH: C, 52.00; H, 5.68; N, 10.90. Found: C, 52.08; H;  
5.70; N, 10.53.

#### Example 20 and Example 21

(+)-1,2,3,6-Tetrahydro-1-{N-[3-(4-(2-pyridyl)-  
20 piperidin-1-yl)-(2-fluoro)propyl]}carboxamido-5-metho  
xycarbonyl-2-oxo-6-(3,4-difluorophenyl)-4-methylpyrim  
idine dihydrochloride

A mixture of (+)-1,2,3,6-tetrahydro-1-{N-[3-  
(4-(2-pyridyl)-piperidine-1-yl)-(2-hydroxy)propyl]}ca  
25 rboxamido-5-methoxycarbonyl-2-oxo-6-(3,4-difluorophen  
yl)-4-methylpyrimidine (0.50 g, 0.92 mmol),  
diethylaminosulfur trifluoride (DAST, 0.222 g, 1.38  
mmol, 1.5 eq.), and benzene (50 mL) was stirred at 70  
°C under dry argon atmosphere for 24 h. The TLC analysis  
30 of reaction mixture showed the complete disappearance  
of the starting material. Solvent was evaporated under  
reduced pressure and the residue was purified by column  
chromatography on silica gel (20 g), using  
chloroform/methanol/2 M ammonia in methanol (500/16/8)  
35 as the eluent to give two products as a mixture of two  
diastereomers. These diastereomers were purified by  
chiral HPLC separation on Chiralpak A3, 4.6 X 250 mm

column, using isocratic condition (90% hexane and 10% ethanol containing 0.5% DEA). The retention time for the first product (example 26) was 12.97 minutes and for the second product (example 27) was 16.18 minutes.

5 The combined yield of these products is (65 mg + 65 mg) 24%. The HCl salt was prepared by treatment with 1N HCl in ether; Example 20: m.p. 132-134 °C;  $[\alpha]_D = +108$  (c = 0.715 g, in 100 mL of chloroform). Anal. Calcd. for  $C_{28}H_{32}N_5O_4F_3Cl_2 \cdot 2.0 H_2O$ : C, 53.38; H, 5.60; N, 11.12.  
10 Found: C, 53.28; H, 5.89; N, 10.96. Example 21: m.p. 130-132 °C;  $[\alpha]_D = +100$  (c = 0.7 g, in 100 mL of chloroform). Anal. Calcd. for  $C_{28}H_{32}N_5O_4F_3Cl_2 \cdot 1.5 H_2O$ : C, 54.15; H, 5.52; N, 11.28. Found: C, 54.17; H, 5.57; N, 11.00.

15 Note: Examples 14 and 15 are two diastereomeric products derived from the (+)enantiomer at the pyrimidine part and the two possible enantiomeric compounds with respect to the fluoromethylene chiral center.

20

#### Example 22

(+)-5-Carboxamido-6-(2,4-difluorophenyl)-4-ethyl-1-{N-[3-(4-cyano-4-phenylpiperidin-1-yl)propyl]} carboxamido-2-oxo-1,2,3,6-tetrahydropyrimidine.

25

#### a) 3-(4-Cyano-4-phenylpiperidin-1-yl)propylphthalimide.

A mixture of 4-cyano-4-phenylpiperidine hydrochloride (111 g, 0.5 mol), 3-bromopropylphthalimide (135.39 g, 0.505 mol), potassium carbonate (276.42 g, 2 mol), and  
30 potassium iodide (5.4 g) in DMF (1 L) was stirred and heated at 100-110 °C for 8 h. About 80% of the solvent was evaporated at reduced pressure, the residue was diluted with dichloromethane (1 L) and washed with brine (3 X 300 mL) and dried ( $Na_2SO_4$ ). Solvent was  
35 evaporated from the dichloromethane solution and the residue was treated with isopropanol (400 mL) and cooled. The pale yellow crystalline product formed was

filtered, washed with ice-cold isopropanol and dried (168.6 g, 90%); M.p. 96-98 °C.

**b) 3-(4-Cyano-4-phenylpiperidin-1-yl)propylamine.**

5 To a solution of 3-(4-cyano-4-phenylpiperidin-1-yl) propylphthalimide (112 g, 0.3 mol) in methanol (1.5 L), hydrazine (30 mL) was added and the mixture was stirred and refluxed for 20 h. It was cooled, the white solid formed was filtered and washed with more  
10 methanol (200 mL). Solvent was evaporated from the filtrate and residue was dried under vacuum for 4 h. Chloroform (500 mL) was added to this, stirred for 1 h and filtered. The white solid was washed with more chloroform (200 mL), the solvent was evaporated from  
15 the combined filtrates to leave the product as an oil (70 g, 96%).

**c) Benzyl 2-[(2,4-difluorophenyl)methylene]-3-oxopentanoate.** A solution of benzyl propionylacetate  
20 (157 g, 0.758 mol), 2,4-difluorobenzaldehyde (107.65 g, 0.758 mol), and piperidinium acetate (5.49 g, 38 mmol) in benzene (1 L) were stirred at room temperature for 96 h. The mixture was washed with water (2 X 100 mL), dried (magnesium sulfate) and the solvent evaporated  
25 under reduced pressure to get the product as a pale yellow syrup (251.2 g). It was used in the next step without further purification.

**d) 5-(Benzyloxycarbonyl)-1,6-dihydro-2-methoxy-4-ethyl-6-(2,4-difluorophenyl)pyrimidine.**

30 A suspension of benzyl 2-[(2,4-difluorophenyl)methylene]-3-oxopentanoate (80.0 g, 0.241 mol), O-methylisourea hemisulfate (63.8 g, 0.362 mol, 1.5 eq.), NaHCO<sub>3</sub> (60.48 g, 0.72 mol) in ethanol (800 mL) was  
35 stirred at 60-70 °C for 20 h. After cooling to room temperature, the mixture was filtered, and the solid was washed with ethanol (200 mL). The solvent was

evaporated from the combined filtrates and the residue was purified by column chromatography ( $\text{SiO}_2$ , EtOAc/Hexane, 10%-30%) to get 5-(benzyloxycarbonyl)-1,6-dihydro-2-methoxy-4-ethyl-6-(2,4-difluorophenyl)pyrimidine as a pale yellow oil (39 g, 42%). The  $^1\text{H}$ -NMR analysis showed it to be a mixture of amine/imine tautomers and was used as is in the next step.

**e) 5-(Benzyloxycarbonyl)-4-ethyl-1,6-dihydro-2-methoxy-6-(2,4-difluorophenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine.**

To a well stirred solution of 5-(benzyloxycarbonyl)-1,6-dihydro-2-methoxy-4-ethyl-6-(2,4-difluorophenyl)pyrimidine (22.5 g, 59.3 mmol) and 4-(N,N-dimethylamino)pyridine (9.3 g, 75.8 mmol) in  $\text{CH}_2\text{Cl}_2$  (200 mL) was added a powder of 4-nitrophenyl chloroformate (15.3 g, 75.8 mmol) at 0 °C. The reaction mixture was stirred for 12 h at room temperature and then water (50 mL) was added. The pH of the aqueous layer was adjusted to 10-11 by the addition of 6 N sodium hydroxide. The dichloromethane layer was separated and dried ( $\text{Na}_2\text{SO}_4$ ). Solvent was evaporated in vacuo and the residue was purified by column chromatography ( $\text{SiO}_2$ , dichloromethane/hexane, 20%-50%) to give the product as a viscous oil (32.0 g, 98%).

**f) 5-(Benzyloxycarbonyl)-4-ethyl-1,6-dihydro-1-{N-[2-phenyl)ethyl]}carboxamido-2-methoxy-6-(2,4-difluorophenyl)pyrimidine.**

To a stirred solution of 5-(benzyloxycarbonyl)-4-ethyl-1,6-dihydro-2-methoxy-6-(2,4-difluorophenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine (32 g, 58.17 mmol) in dichloromethane (200 mL) was added R-(+)- $\alpha$ -methylbenzylamine (9.16, 75.6 mmol) at room temperature and the stirring was continued for 12 h. The mixture was diluted with more dichloromethane (200 mL) and washed with 0.5 N NaOH solution (2 x 60 mL). The

organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered and solvent was evaporated. The resulting mixture of diastereomers was separated by column chromatography( $\text{SiO}_2$ , 3% EtOAc in toluene). The first major product to elute was (+)-5-(benzyloxycarbonyl)-4-ethyl-1,6-dihydro-1-{N-[2-phenyl)ethyl]}carboxamido-2-methoxy-6-(2,4-difluorophenyl)pyrimidine (12.15 g, 38%).  $[\alpha]_D = +214$  (c = 1.5 g in 100 mL  $\text{CHCl}_3$ ); The second major product to elute was the other diastereomer and no effort was made to isolate it.

**g) (+)-5-(Benzyloxycarbonyl)-1,6-dihydro-2-methoxy-4-ethyl-6-(2,4-difluorophenyl)pyrimidine.**

To a stirred solution of (+)-5-(benzyloxycarbonyl)-4-ethyl-1,6-dihydro-1-{N-[2-phenyl)ethyl]}carboxamido-2-methoxy-6-(2,4-difluorophenyl)pyrimidine (11.15 g, 20.41 mmol) in toluene (250 mL) was added 1,8-diazabicyclo[5,4,0]-undec-7-ene (4.04 g, 26.53 mmol) and the mixture was stirred at room temperature for 14 h. The solvent was evaporated and the residue was purified by flash column chromatography on silica gel with 3:1 EtOAc/hexane as eluent to give (+)-5-(benzyloxycarbonyl)-1,6-dihydro-2-methoxy-4-ethyl-6-(2,4-difluorophenyl)pyrimidine as a viscous oil (6.15 g, 78%).

**h) (+)-5-(Benzyloxycarbonyl)-4-ethyl-1,6-dihydro-2-methoxy-6-(2,4-difluorophenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine.**

To a well stirred solution of (+)-5-(benzyloxycarbonyl)-1,6-dihydro-2-methoxy-4-ethyl-6-(2,4-difluorophenyl)pyrimidine (4.1 g, 10.62 mmol) and 4-(N,N-dimethylamino)pyridine (1.69 g, 13.80 mmol) in  $\text{CH}_2\text{Cl}_2$  (200 mL) was added a powder of 4-nitrophenyl chloroformate (2.78 g, 13.80 mmol) at room temperature. The reaction mixture was stirred for 12 h and washed with 0.5 N NaOH solution (2 X 50 mL). The organic layer

was separated and dried ( $\text{Na}_2\text{SO}_4$ ). The solvent was evaporated and the residue was purified by column chromatography on silica gel using dichloromethane/hexane (20%-50%) as the eluent to give  
5 (+)-5-(benzyloxycarbonyl)-4-ethyl-1,6-dihydro-2-methoxy-6-(2,4-difluorophenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine (5.37 g, 92%) as a viscous oil.

10 i) (+)-5-(Benzyloxycarbonyl)-6-(2,4-difluorophenyl)-4-ethyl-1-{N-[3-(4-cyano-4-phenylpiperidin-1-yl)propyl]}carboxamido-2-oxo-1,2,3,6-tetrahydropyrimidine.

A mixture of (+)-5-(benzyloxycarbonyl)-4-ethyl-1,6-dihydro-2-methoxy-6-(2,4-difluorophenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine (6.50 g, 11.81 mmol)  
15 and 3-[4-cyano-4-phenylpiperidin-1-yl]propylamine (3.60 g, 15.36 mmol) in THF (500 mL) was stirred at room temperature for 18 h. It was cooled to 0 °C and 10% HCl in water (2 mL) was added and stirred for 2 h. The  
20 mixture was washed with 0.5 N aq. NaOH solution (30 mL), dried over  $\text{Na}_2\text{SO}_4$  and the solvent evaporated. The residue was purified by column chromatography on  $\text{SiO}_2$  using  $\text{CHCl}_3/\text{MeOH}/2\text{M NH}_3$  in MeOH (100/2/1) as eluent to obtain  
25 (+)-5-(benzyloxycarbonyl)-6-(2,4-difluorophenyl)-4-ethyl-1-{N-[3-(4-cyano-4-phenylpiperidin-1-yl)propyl]}carboxamido-2-oxo-1,2,3,6-tetrahydropyrimidine as a white foamy solid (7.05 g, 93%).

30 j) 6-(2,4-Difluorophenyl)-4-ethyl-1-{N-[3-(4-cyano-4-phenylpiperidin-1-yl)propyl]}carboxamido-1,2,3,6-tetrahydro-2-oxopyrimidine-5-carboxylic acid.

To a suspension of 10% Pd-C (2.1 g) in MeOH (100 mL)  
35 and  $\text{H}_2\text{O}$  (20 mL) was added a solution of (+)-5-(benzyloxycarbonyl)-6-(2,4-difluorophenyl)-4-ethyl-1-{N-[3-(4-cyano-4-phenylpiperidin-1-yl)propyl]}

carboxamido-2-oxo-1,2,3,6-tetrahydropyrimidine (7.55 g, 11.2 mL) in methanol (100 mL) and the mixture was hydrogenated at 80 psi for 14 h. The black suspension was filtered through a pad of celite and washed thoroughly with MeOH (2.0 L) and methanol/chloroform (1:2, 200 mL). Solvent was evaporated from the combined filtrate to leave the product (+)-6-(2,4-difluorophenyl)-4-ethyl-1-{N-[3-(4-cyano-4-phenylpiperidin-1-yl)propyl]}carboxamido-1,2,3,6-tetrahydro-2-oxopyrimidine-5-carboxylic acid as a white solid (6.06 g, 98%). It was used in the next step without further purification.

k) (+)-5-Carboxamido-6-(2,4-difluorophenyl)-4-ethyl-1-{N-[3-(4-cyano-4-phenylpiperidin-1-yl)propyl]}carboxamido-2-oxo-1,2,3,6-tetrahydropyrimidine.

A mixture of (+)-6-(2,4-difluorophenyl)-4-ethyl-1-{N-[3-(4-cyano-4-phenylpiperidin-1-yl)propyl]}carboxamido-1,2,3,6-tetrahydro-2-oxopyrimidine-5-carboxylic acid (6.30 g, 11.18 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (4.29 g, 22.36 mmol, 2 eq.), and 4-(N,N-dimethylamino)pyridine (3.41 g, 27.95 mmol, 2.5 eq) in anhydrous dichloromethane (400 mL) was stirred at room temperature for 2 h. To this, 40% aqueous ammonia (6.13 g, 5 eq) was added and the stirring was continued for 12 h. The mixture was diluted with 200 mL of dichloromethane and washed with saturated aqueous ammonium chloride solution (3 X 200 mL). Solvent was evaporated from the dried (sodium sulfate) dichloromethane solution and the residue was purified by column chromatography on silica gel using chloroform-methanol-2M ammonia in methanol (100/2/1) as the eluent, to obtain the desired product as a white powder (5.45 g, 87%); m.p. 210-211 °C; Part of the compound (300 mg) was dissolved in dichloromethane (3 mL), cooled to 0-5 °C and treated with 1N HCl in ether

(10 mL) followed by anhydrous ether (20 mL). The white powder formed was filtered, washed with ether (100 mL) and dried (320 mg, 100%); m.p. 196-97 °C;  $[\alpha]_D = +126$  ( $c = 0.505$  g, in 100 mL of 1:1 chloroform/MeOH). Anal.

5 Calcd. for  $C_{29}H_{33}N_6O_3F_2Cl$ : C, 59.27; H, 5.78; N, 14.24. Found: C, 59.33; H, 5.67; N, 14.32.

### Example 23

(+) - 5 - Carboxamido - 6 - (3,4-difluorophenyl) - 4 - methoxymethyl - 1 - {N - [3 - (4(2-pyridyl)piperidin-1-yl) propyl]}carboxamido - 2 - oxo - 1,2,3,6-tetrahydropyrimidine dihydrochloride.

10

#### a) 2-Cyanoethyl 4-methoxyacetoacetate.

A mixture of methyl 4-methoxyacetoacetate (50 g, 0.342 mol) and 3-hydroxypropionitrile (31.61 g, 0.444 mol) was heated to 160-180 °C in a distillation set-up. It was kept at that temperature for 2 h until the distillation of the methanol stopped. The residual yellow oil of 2-cyanoethyl 4-methoxyacetoacetate (56.4 g, 90%) was used as is without any further purification.

15

20

#### b) 2-Cyanoethyl 2-[(3,4-difluorophenyl)methylene]-3-oxo-4-methoxybutyrate.

A solution of 2-cyanoethyl 4-methoxyacetoacetate (17.8 g, 0.125 mol), 3,4-difluorobenzaldehyde (25.5 g, 6.26 mmol), acetic acid (0.376 g, 6.26 mmol), and piperidine (0.533 g, 6.26 mmol) in benzene (500 mL) were added molecular sieves (200 g) and the mixture was stirred at room temperature for 24 h. Then the solvent was evaporated under reduced pressure and the residue was purified by column chromatography using chloroform/ethyl acetate (100:5) to get the product as an oil (29 g, 75%).

25

30

35

#### c) 5-(2-Cyanoethoxycarbonyl)-1,6-dihydro-2-methoxy-4-methoxymethyl-6-(3,4-difluorophenyl)pyrimidine.



A suspension of 2-cyanoethyl 2-[(3,4-difluorophenyl)methylene]-3-oxo-4-methoxybutyrate (29 g, 0.094 mol), O-methylisourea hemisulfate (21 g, 0.121 mol, 1.3 eq.), dimethylaminopyridine (29.67 g, 0.243 mol, 2.5 eq.) in ethanol (400 mL) was stirred at 50-55 °C for 6 h. The solvent was evaporated from the combined filtrates and the residue was purified by column chromatography (SiO<sub>2</sub>, EtOAc/hexane, 10%-30%) to get 5-(2-cyanoethoxycarbonyl)-1,6-dihydro-2-methoxy-4-methoxymethyl-6-(3,4-difluorophenyl)pyrimidine as a pale yellow oil (10.5 g, 31%). The <sup>1</sup>H-NMR analysis showed it to be a mixture of amine/imine tautomers and was used as is in the next step.

d) 5-(2-Cyanoethoxycarbonyl)-4-methoxymethyl-1,6-dihydro-2-methoxy-6-(3,4-difluorophenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine.

To a well stirred solution of 5-(2-cyanoethoxycarbonyl)-1,6-dihydro-2-methoxy-4-methoxymethyl-6-(3,4-difluorophenyl)pyrimidine (10.5 g, 28.74 mmol) and 4-(N,N-dimethylamino)pyridine (6.95 g, 34.49 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) was added a powder of 4-nitrophenyl chloroformate (4.21 g, 34.49 mmol) at 0 °C. The reaction mixture was stirred for 12 h at room temperature and then the solvent was evaporated. The residue was purified by column chromatography (SiO<sub>2</sub>, dichloromethane/hexane, 20%-50%) to give the product as a viscous oil (6.5 g, 43%).

e) 5-(2-Cyanoethoxycarbonyl)-4-methoxymethyl-1,6-dihydro-1-{N-[2-phenyl)ethyl]}carboxamido-2-methoxy-6-(3,4-difluorophenyl)pyrimidine.

To a stirred solution of 5-(2-cyanoethoxycarbonyl)-4-methoxymethyl-1,6-dihydro-2-methoxy-6-(3,4-difluorophenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine (6.5 g, 12.25 mmol) in dichloromethane (150 mL) was added R-(+)-α-methylbenzylamine (1.78 g, 14.7

mmol) at room temperature and the stirring was continued for 12 h. Solvent was evaporated and the residue was purified by column chromatography (SiO<sub>2</sub>, 10-20% EtOAc in hexane). The first major product to elute was (+)-5-(2-cyanoethoxycarbonyl)-4-methoxymethyl-1,6-dihydro-1-{N-[2-phenyl]ethyl}carboxamido-2-methoxy-6-(3,4-difluorophenyl)pyrimidine (2.54 g, 44.5%).  $[\alpha]_D = +177.8$  (c = 9.2 g in 100 mL CHCl<sub>3</sub>); The second major product to elute was the other diastereomer and no effort was made to isolate it.

**f) (+)-5-(2-Cyanoethoxycarbonyl)-1,6-dihydro-2-methoxy-4-ethyl-6-(3,4-difluorophenyl)pyrimidine.**

To a stirred solution of (+)-5-(2-cyanoethoxycarbonyl)-4-methoxymethyl-1,6-dihydro-1-{N-[2-phenyl]ethyl}carboxamido-2-methoxy-6-(3,4-difluorophenyl)pyrimidine (2.80 g, 5.46 mmol) in toluene (80 mL) was added 1,8-diazabicyclo[5,4,0]-undec-7-ene (0.250 g, 1.64 mmol) and the mixture was stirred at 75 °C for 1 h. The solvent was evaporated and the residue was purified by flash column chromatography on silica gel with 3:1 EtOAc/hexane as eluent to give (+)-5-(2-cyanoethoxycarbonyl)-1,6-dihydro-2-methoxy-4-methoxymethyl-6-(3,4-difluorophenyl)pyrimidine as a viscous oil (0.82 g, 40.5%).

**g) (+)-5-(2-Cyanoethoxycarbonyl)-4-methoxymethyl-1,6-dihydro-2-methoxy-6-(3,4-difluorophenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine.**

To a well stirred solution of (+)-5-(2-cyanoethoxycarbonyl)-1,6-dihydro-2-methoxy-4-methoxymethyl-6-(3,4-difluorophenyl)pyrimidine (0.82 g, 2.24 mmol) and 4-(N,N-dimethylamino)pyridine (0.329 g, 2.69 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (200 mL) was added a powder of 4-nitrophenyl chloroformate (0.543 g, 2.69 mmol) at room temperature. The solvent was evaporated and the residue was purified by column chromatography on silica

gel using dichloromethane/hexane (20%-50%) as the eluent to give (+)-5-(2-cyanoethoxycarbonyl)-4-methoxymethyl-1,6-dihydro-2-methoxy-6-(3,4-difluorophenyl)-1-[(4-nitrophenoxy)carbonyl]pyrimidine (0.80 g, 67%) as a viscous oil.

h) (+)-5-(2-Cyanoethoxycarbonyl)-6-(3,4-difluorophenyl)-4-methoxymethyl-1-{N-[3-(4-(2-pyridyl)piperidin-1-yl)propyl]}carboxamido-2-oxo-1,2,3,6-tetrahydropyrimidine.

A mixture of (+)-5-(2-cyanoethoxycarbonyl)-4-methoxymethyl-1,6-dihydro-2-methoxy-6-(3,4-difluorophenyl)-1-[(4-nitrophenoxy)carbonyl]pyrimidine (0.44 g, 0.83 mmol) and 3-[4-(2-pyridyl)piperidin-1-yl]propylamine (0.218 g, 0.996 mmol) in THF (15 mL) was stirred at room temperature for 12 h. It was cooled to 0 °C and 10% HCl in water (2 mL) was added and stirred for 2 h. Solvent was evaporated and the residue was purified by column chromatography on SiO<sub>2</sub> using CHCl<sub>3</sub>/MeOH/2M NH<sub>3</sub> in MeOH (100/2/1) as eluent to obtain (+)-5-(2-cyanoethoxycarbonyl)-6-(3,4-difluorophenyl)-4-methoxymethyl-1-{N-[3-(4-(2-pyridyl)piperidin-1-yl)propyl]}carboxamido-2-oxo-1,2,3,6-tetrahydropyrimidine as a white foamy solid (0.41 g, 83%).

i) 6-(3,4-Difluorophenyl)-4-methoxymethyl-1-{N-[3-(4-(2-pyridyl)piperidin-1-yl)propyl]}carboxamido-1,2,3,6-tetrahydro-2-oxopyrimidine-5-carboxylic acid.

To a stirred solution of (+)-5-(2-cyanoethoxycarbonyl)-6-(3,4-difluorophenyl)-4-methoxymethyl-1-{N-[3-(4-(2-pyridyl)piperidin-1-yl)propyl]}carboxamido-2-oxo-1,2,3,6-tetrahydropyrimidine (0.34 g, 0.57 mmol) in acetone (5 mL) at 0 °C, sodium hydroxide solution (1 N, 1.71 mL) was added drop wise and the stirring was continued until the disappearance of the starting

material (1 hour). Most of the acetone from the mixture was evaporated under reduced pressure while keeping the temperature at 0 °C and the residue was adjusted to pH 7.0 by the addition of 1N hydrochloric acid. The white precipitate of 6-(3,4-difluorophenyl)-4-methoxymethyl-1-{N-[3-(4-(2-pyridyl)piperidin-1-yl)propyl]}carboxamido-1,2,3,6-tetrahydro-2-oxopyrimidine-5-carboxylic acid formed was filtered and dried under vacuum (0.30 g, 96%).

j) (+)-5-Carboxamido-6-(3,4-difluorophenyl)-4-methoxymethyl-1-{N-[3-(4-(2-pyridyl)piperidin-1-yl)propyl]}carboxamido-2-oxo-1,2,3,6-tetrahydropyrimidine.

A mixture of (+)-6-(3,4-difluorophenyl)-4-methoxymethyl-1-{N-[3-(4-(2-pyridyl)piperidin-1-yl)propyl]}carboxamido-1,2,3,6-tetrahydro-2-oxopyrimidine-5-carboxylic acid (0.30 g, 0.55 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.212 g, 1.1 mmol, 2 eq.), and 4-(N,N-dimethylamino)pyridine (0.134 g, 1.1 mmol, 2 eq) in anhydrous dichloromethane (20 mL) was stirred at room temperature for 2 h. To this, 40% aqueous ammonia (0.64 g, 10 eq) was added and the stirring was continued for 12 h. The mixture was diluted with 20 mL of dichloromethane and washed with saturated aqueous ammonium chloride solution (3 X 200 mL). Solvent was evaporated from the dried (sodium sulfate) dichloromethane solution and the residue was purified by column chromatography on silica gel using chloroform-methanol-2M ammonia in methanol (100/2/1) as the eluent, to obtain the desired product as a white powder (0.232 g, 78%); The HCl salt of this compound was prepared by treatment with 1 N HCl in ether. m.p. 95-97 °C;  $[\alpha]_D = +139$  (c = 2.1 g, in 100 mL of chloroform). Anal. Calcd. for  $C_{27}H_{34}N_6O_4F_2Cl_2 \cdot 2.2 H_2O$ : C,

49.50; H, 5.91; N, 12.83. Found: C, 49.50; H, 5.89; N, 12.43.

**Example 24**

5      (+) - 5-Methoxycarbonyl-6-(3,4-difluorophenyl)-4-methoxymethyl-1-{N-[3-(4-(2-pyridyl)piperidin-1-yl)propyl]}carboxamido-2-oxo-1,2,3,6-tetrahydropyrimidine.

10      A mixture of (+)-6-(3,4-difluorophenyl)-4-methoxymethyl-1-{N-[3-(4-(2-pyridyl)piperidin-1-yl)propyl]}carboxamido-1,2,3,6-tetrahydro-2-oxopyrimidine-5-carboxylic acid (0.30 g, 0.55 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.212 g, 1.1 mmol, 2 eq.), and 4-(N,N-dimethylamino)pyridine (0.134 g, 1.1 mmol, 2 eq) in methanol (20 mL) was stirred at room temperature for 20 h. Solvent was evaporated and the residue was dissolved in 20 mL of dichloromethane and washed with saturated aqueous ammonium chloride solution (3 X 200 mL). Solvent was evaporated from the dried (sodium sulfate) dichloromethane solution and the residue was purified by column chromatography on silica gel using chloroform-methanol-2M ammonia in methanol (100/2/1) as the eluent, to obtain the desired product as a white powder (278 mg, 91%); The HCl salt of this compound was prepared by treatment with 1 N HCl in ether. m.p. 180-184 °C;  $[\alpha]_D = +122$  (c = 1.25 g, in 100 mL of methanol). Anal. Calcd. for  $C_{28}H_{35}N_5O_5F_2Cl_2 \cdot 1.0 H_2O$ : C, 51.86; H, 5.75; N, 10.80. Found: C, 52.14; H, 5.72; N, 10.53.

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**Example 25**

35      (+) - 1,2,3,6-Tetrahydro-1-{N-[3-(4-(2-pyridyl)-piperidine-1-yl)-(2-oxo)propyl]}carboxamido-5-methoxycarbonyl-2-oxo-6-(3,4-difluorophenyl)-4-methoxymethylpyrimidine dihydrochloride

a) Methyl 2-[(3,4-difluorophenyl) methylene]-3-oxo-4-

**methoxybutyrate.**

A solution of methyl 4-methoxyacetoacetate (84.32 g, 0.577 mol), 3,4-difluorobenzaldehyde (82 g, 0.577 mmol), and piperidinium acetate (5.86 g, 0.068 mol) in benzene (1.5 L) were added molecular sieves (400 g) and the mixture was stirred at room temperature for 48 h. The molecular sieves were removed by filtration and the solvent was evaporated from the filtrate under reduced pressure. The residue was purified by column chromatography on silica gel using chloroform/ethyl acetate (100:3) to get the product as an oil (67 g, 47%).

**b) 5-Methoxycarbonyl-1,6-dihydro-2-methoxy-4-methoxymethyl-6-(3,4-difluorophenyl)pyrimidine.**

A suspension of methyl 2-[(3,4-difluorophenyl)methylene]-3-oxo-4-methoxybutyrate (7.50 g, 27.75 mmol), O-methylisourea hemisulfate (7.17 g, 41.63 mmol, 1.5 eq.), sodium bicarbonate (6.99 g, 83.25 mmol, 3 eq.) in ethanol (400 mL) was stirred at 50-55 °C for 6 h. The solvent was evaporated from the combined filtrates and the residue was purified by column chromatography (SiO<sub>2</sub>, EtOAc/hexane, 10%-30%) to get 5-methoxycarbonyl-1,6-dihydro-2-methoxy-4-methoxymethyl-6-(3,4-difluorophenyl)pyrimidine as a pale yellow oil (4.3 g, 47%). The <sup>1</sup>H-NMR analysis showed it to be a mixture of amine/imine tautomers and was used as is in the next step.

**c) 5-Methoxycarbonyl-4-methoxymethyl-1,6-dihydro-2-methoxy-6-(3,4-difluorophenyl)-1-[(4-nitrophenoxy)carbonyl]pyrimidine.**

To a well stirred solution of 5-methoxycarbonyl-1,6-dihydro-2-methoxy-4-methoxymethyl-6-(3,4-difluorophenyl)pyrimidine (4.3 g, 13.18 mmol) and 4-(N,N-dimethylamino)pyridine (2.09 g, 17.13 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) was added a powder of 4-nitrophenyl

chloroformate (3.45 g, 17.13 mmol) at 0 °C. The reaction mixture was stirred for 12 h at room temperature and the solid formed was removed by filtration. Solvent was evaporated from the filtrate and the residue was purified by column chromatography (SiO<sub>2</sub>, dichloromethane/hexane, 20%-50%) to give the product as a viscous oil (3.85 g, 59%).

d) **5-Methoxycarbonyl-4-methoxymethyl-1,6-dihydro-1-{N-[2-phenyl)ethyl]}carboxamido-2-methoxy-6-(3,4-difluorophenyl)pyrimidine.**

To a stirred solution of 5-methoxycarbonyl-4-methoxymethyl-1,6-dihydro-2-methoxy-6-(3,4-difluorophenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine (3.82 g, 7.77 mmol) in THF (140 mL) was added R-(+)- $\alpha$ -methylbenzylamine (1.13 g, 9.33 mmol, 1.2 eq.) at room temperature and the stirring was continued for 12 h. Solvent was evaporated and the residue was purified by column chromatography (SiO<sub>2</sub>, 10-20% EtOAc in hexane). The first major product to elute was (+)-5-methoxycarbonyl-4-methoxymethyl-1,6-dihydro-1-{N-[2-phenyl)ethyl]}carboxamido-2-methoxy-6-(3,4-difluorophenyl)pyrimidine (1.74 g, 44.5%).  $[\alpha]_D^{25} = +205.5$  (c = 5.1 g in 100 mL CHCl<sub>3</sub>); The second major product to elute was the other diastereomer and no effort was made to isolate it.

e) **(+)-5-Methoxycarbonyl-1,6-dihydro-2-methoxy-4-methoxymethyl-6-(3,4-difluorophenyl)pyrimidine.**

To a stirred solution of (+)-5-methoxycarbonyl-4-methoxymethyl-1,6-dihydro-1-{N-[2-phenyl)ethyl]}carboxamido-2-methoxy-6-(3,4-difluorophenyl)pyrimidine (1.74 g, 3.67 mmol) in toluene (40 mL) was added 1,8-diazabicyclo[5,4,0]-undec-7-ene (0.250 g, 1.64 mmol) and the mixture was stirred at 70-80 °C for 1.5 h. The solvent was evaporated and the residue was purified by flash column chromatography on silica gel with 9:1

CHCl<sub>3</sub>/EtOAc as eluent to give (+)-5-methoxycarbonyl-1,6-dihydro-2-methoxy-4-methoxymethyl-6-(3,4-difluorophenyl)pyrimidine as a viscous oil (1.11 g, 92.5%).

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**f) (+)-5-Methoxycarbonyl-4-methoxymethyl-1,6-dihydro-2-methoxy-6-(3,4-difluorophenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine.**

10 To a well stirred solution of (+)-5-methoxycarbonyl-1,6-dihydro-2-methoxy-4-methoxymethyl-6-(3,4-difluorophenyl)pyrimidine (1.11 g, 3.4 mmol) and 4-(N,N-dimethylamino)pyridine (0.54 g, 4.42 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (200 mL) was added a powder of 4-nitrophenyl chloroformate (0.891 g, 4.42 mmol) at room temperature.

15 The solvent was evaporated and the residue was purified by column chromatography on silica gel using CHCl<sub>3</sub>/EtOAc (20%-50%) as the eluent to give (+)-5-methoxycarbonyl-4-methoxymethyl-1,6-dihydro-2-methoxy-6-(3,4-difluorophenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine (1.30 g, 78%) as a viscous oil.  $[\alpha]_D = +262.2$  (c = 2.3 g in 100 mL CHCl<sub>3</sub>).

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**g) (+)-1,2,3,6-Tetrahydro-1-{N-[3-(4-(2-pyridyl)-piperidine-1-yl)-(2-hydroxy)propyl]}carboxamido-5-methoxycarbonyl-2-oxo-6-(3,4-difluorophenyl)-4-methoxymethylpyrimidine.**

25

A solution of (+)-6-(3,4-difluorophenyl)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methoxymethyl-1-(4-nitrophenoxy)carbonylpyrimidine (0.450 g, 0.91 mmol), 3-[4-(2-pyridyl)piperidin-1-yl]-2-hydroxypropylamine (0.280 g, 1.19 mmol) in tetrahydrofuran (100 mL) was stirred at room temperature for 24 hours. The reaction mixture was stirred for another 1 hour after addition of 2 ml of 6N HCl. Solvent was evaporated at reduced pressure and the residue was basified by treatment with 10% aqueous KOH solution, extracted with dichloromethane (3 x 10 mL). The combined extracts

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35



were dried over potassium carbonate, and solvent evaporated. The crude product was purified by flash chromatography (dichloromethane:MeOH:2M ammonia in MeOH,90:8:4) to give 0.514 g (98%) as a syrup.

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h) (+)-1,2,3,6-Tetrahydro-1-{N-[3-(4-(2-pyridyl)-piperidine-1-yl)-(2-oxo)propyl]}carboxamido-5-methoxycarbonyl-2-oxo-6-(3,4-difluorophenyl)-4-methoxymethylpyrimidine dihydrochloride

10

To a stirred solution of DMSO (0.174 g, 2.23 mmol) in dichloromethane (5 mL) at -78 °C, oxalyl chloride (0.135 g, 1.07 mmol) in dichloromethane (5 mL) was added and the mixture was stirred for 3 min. To this, a solution of

15

(+)-1,2,3,6-tetrahydro-1-{N-[3-(4-(2-pyridyl)-piperidine-1-yl)-(2-hydroxy)propyl]}carboxamido-5-methoxycarbonyl-2-oxo-6-(3,4-difluorophenyl)-4-methoxymethylpyrimidine (0.51 g, 0.889 mmol) in dichloromethane (5 mL) was added and the stirring was continued for 15 min. It was warmed to room temperature and added 5 mL

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of water. The pH of the mixture was adjusted to 10-11 by adding 1N NaOH and the dichloromethane layer was separated. The aqueous layer was extracted with more dichloromethane (3 X 10 mL). The combined

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dichloromethane extracts were dried (magnesium sulfate), solvents evaporated, and the residue was purified by flash chromatography (dichloromethane:MeOH:2M ammonia in MeOH,90:8:4) to give 0.32 g (63%) of the product as a syrup.  $[\alpha]_D = +122$  (c = 0.55 g in 100 mL  $\text{CHCl}_3$ ); Anal. Calcd. for

30

$\text{C}_{29}\text{H}_{33}\text{N}_5\text{O}_6\text{F}_2\text{Cl}_2 \cdot 2.5 \text{ H}_2\text{O}$ : C, 48.77; H, 5.55; N, 10.16. Found: C, 48.71; H, 5.72; N, 9.87.

#### Example 26 and Example 27

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Syn and anti isomers of (+)-1,2,3,6-tetrahydro-1-{N-[3-(4-(2-pyridyl)-piperidine-1-yl)-(2-hydroximino)propyl]}carboxamido-5-methoxycarbonyl-2-oxo-6-(3,4-difluorophenyl)-4-methoxymethylpyrimidine dihydrochloride

A solution of (+)-1,2,3,6-tetrahydro-1-{N-[3-(4-(2-pyridyl)-piperidin-1-yl)-(2-oxo)propyl]}carboxamido-5-methoxycarbonyl-2-oxo-6-(3,4-difluorophenyl)-4-methoxymethylpyrimidine (0.14 g, 0.22 mmol),  
5 hydroxylamine hydrochloride (19.6 mg, 0.28 mmol), and sodium acetate (74.8 mg, 0.55 mmol) in methanol (5 mL) was stirred at room temperature for 24 h. Solvent was evaporated at reduced pressure, the residue was mixed with dichloromethane (30 mL) and washed with water.  
10 The dichloromethane solution was dried (sodium sulfate) and the solvent evaporated. The residue was purified by column chromatography on silica gel (chloroform:MeOH:2M ammonia in MeOH, 90:8:4). The first product to elute was Example 26, syn isomer with  
15 respect to oxime hydroxyl and piperidine (30 mg);  $[\alpha]_D = +94.1$  (c = 0.528 g in 100 mL  $\text{CHCl}_3$ ); The HCl salt was prepared by treatment with 1N HCl in ether; m.p. 90-92 °C; Anal. Calcd. for  $\text{C}_{28}\text{H}_{34}\text{N}_6\text{O}_6\text{F}_2\text{Cl}_2 \cdot 1.5 \text{H}_2\text{O} \cdot 0.6 \text{CH}_2\text{Cl}_2$ : C, 47.65; H, 5.35; N, 11.26. Found: C, 47.67; H, 5.56; N,  
20 11.36.

The second product to elute was example 33, anti isomer with respect to oxime hydroxyl and piperidine (70 mg);  $[\alpha]_D = +104$  (c = 0.3 g in 100 mL  $\text{CHCl}_3$ ); The HCl salt  
25 was prepared by treatment with 1N HCl in ether; m.p. 103-105 °C; Anal. Calcd. for  $\text{C}_{28}\text{H}_{34}\text{N}_6\text{O}_6\text{F}_2\text{Cl}_2 \cdot 2.2 \text{H}_2\text{O} \cdot 0.22 \text{CH}_2\text{Cl}_2$ : C, 47.74; H, 5.51; N, 11.84. Found: C, 48.01; H, 5.72; N, 11.57.

### 30 Example 28

(+)-1,2,3,6-Tetrahydro-1-{N-[3-(4-(2-pyridyl)-piperidine-1-yl)-(2-methoximino)propyl]}carboxamido-5-methoxycarbonyl-2-oxo-6-(3,4-difluorophenyl)-4-methoxymethylpyrimidine dihydrochloride

35 A solution of (+)-1,2,3,6-tetrahydro-1-{N-[3-(4-(2-pyridyl)-piperidine-1-yl)-(2-oxo)propyl]}carboxamido-5-methoxycarbonyl-2-oxo-6-(3,4-difluorophenyl)-

4-methoxymethylpyrimidine (30 mg, 0.047 mmol), O-methoxylamine hydrochloride (7.78 mg, 0.093 mmol), and sodium acetate (32 mg, 0.24 mmol) in methanol (5 mL) was stirred at room temperature for 24 h. Solvent was  
5 evaporated at reduced pressure, the residue was mixed with dichloromethane (30 mL) and washed with water. The dichloromethane solution was dried (sodium sulfate) and the solvent evaporated. The residue was purified by column chromatography on silica gel  
10 (chloroform:MeOH:2M ammonia in MeOH, 90:8:4). Only one isomeric product was detected by this purification (20 mg, 71%);  $[\alpha]_D = +98$  (c = 0.4 g in 100 mL  $\text{CHCl}_3$ ); The HCl salt was prepared by treatment with 1N HCl in ether; m.p. 109-112 °C; Anal. Calcd. for  
15  $\text{C}_{29}\text{H}_{36}\text{N}_6\text{O}_6\text{F}_2\text{Cl}_2 \cdot 2.3\text{H}_2\text{O} \cdot 0.46 \text{CH}_2\text{Cl}_2$ : C, 46.93; H, 5.55; N, 11.15. Found: C, 47.08; H, 5.66; N, 10.88.

#### Example 29

(±) - 1, 2, 3, 6 - Tetrahydro - 1 - { N - [ 3 -  
20 (4 - (2-carboxamidophenyl) - piperazin-1-yl) - propyl ] } carb  
oxamido-5-acetyl-2-oxo-6 - (3,4,5-trifluorophenyl) - 4-me  
thylpyrimidine dihydrochloride

a) 3 - { (3,4,5-Trifluorophenyl)methylene } - 2,4 -  
25 pentanedione.

A mixture of 3,4,5-trifluorobenzaldehyde (4.2 g, 26.2 mmol), 2,4-pentanedione (2.62 g, 26.2 mmol), piperidine (0.430 g, 5 mmol) in benzene (150 mL) was stirred and refluxed with a Dean-Stark trap for 8 hours. Benzene  
30 was evaporated, the yellow oily residue, 2 - { (3,4,5-trifluorophenyl)methylene } - 2,4-pentanedione, was used in the next step without any further purification.

b) 6 - (3,4,5-Trifluorophenyl) - 1,6-dihydro-2-methoxy-  
35 5-acetyl-4-methylpyrimidine.

A mixture of 2 - { (3,4,5-trifluorophenyl)methylene } - 2,4-pentanedione (26.2 mmol), O-methylisourea hydrogen

sulfate (3.22 g, 39.3 mmol), and NaHCO<sub>3</sub> (6.6 g, 78.6 mmol) in EtOH (400 mL) was stirred and heated at 95-100 °C for 6 hours. The mixture was filtered, the solid residue was washed with ethanol (100 mL). Solvent was evaporated from the combined filtrate and the crude product was purified by flash column chromatography on silica gel using 10% through 25% EtOAc in hexane as the gradient eluent, to leave the product as an oil (2.80 g, 36%).

c) **6-(3,4,5-Trifluorophenyl)-1,6-dihydro-2-methoxy-5-acetyl-4-methyl-1-[(4-nitrophenyloxy)carbonyl]pyrimidine**

To a solution of 6-(3,4,5-trifluorophenyl)-1,6-dihydro-2-methoxy-5-acetyl-4-methylpyrimidine (2.8 g, 9.38 mmol) and pyridine (10 mL) in CH<sub>2</sub>Cl<sub>2</sub> (200 mL) at 0-5 °C, 4-nitrophenyl chloroformate (1.886 g, 9.38 mmol) was added and the mixture was allowed to warm to room temperature. After 12 hours solvent was evaporated and the residue was purified by flash column chromatography (SiO<sub>2</sub>, dichloromethane/EtOAc, 10%-15%) to obtain the product as a white powder (4.0 g, 92%).

d) **6-(3,4,5-Trifluorophenyl)-1,2,3,6-tetrahydro-2-oxo-5-acetyl-4-methyl-1-[(4-nitrophenyloxy)carbonyl]pyrimidine.**

To a well-stirred solution of 6-(3,4,5-trifluorophenyl)-1,6-dihydro-2-methoxy-5-acetyl-4-methyl-1-[(4-nitrophenyloxy)carbonyl]pyrimidine (4.0 g, 8.63 mmol) in THF (100 mL) at 0-5 °C, 6N aqueous HCl (4 mL) was added and the mixture was allowed to warm to room temperature. After 2 h, solvent was evaporated and the product dried under vacuum. The product was obtained as a pure single component and no need for further purification (3.88 g, 100%).

e) **(±)-1,2,3,6-Tetrahydro-1-{N-[3-**

(4-(2-carboxamidophenyl)-piperazin-1-yl)-propyl}carb  
oxamido-5-acetyl-2-oxo-6-(3,4,5-trifluorophenyl)-4-me  
thylpyrimidine dihydrochloride

5 A mixture of 6-(3,4,5-difluorophenyl)-1,2,3,6-tetra  
hydro-2-oxo-5-acetyl-4-methyl-1-[(4-nitrophenoxy)  
carbonyl]pyrimidine (44.9 mg, 0.1 mmol) and 3-  
[4-(2-carboxamidophenyl)-piperazin-1-yl]-propylamine  
(26.2 mg, 0.1 mmol) in THF (10 mL) was stirred at room  
10 temperature for 10 h and the solvent evaporated. It  
was redissolved in dichloromethane (10 mL), washed with  
ice-cold 0.5 N NaOH (2 X 5 mL), dried and solvent  
evaporated. The residue was purified by preparative  
thin layer chromatography on silica gel using  
15 chloroform-methanol-2M ammonia in methanol (100/2/1) as  
the eluent to afford the product as a white powder (60  
mg, 93%); The HCl salt was prepared by treatment with  
1N HCl in ether to give the product as a  
dihydrochloride salt. Anal. Calcd. for  $C_{28}H_{33}N_6O_4Cl_2F_3 \cdot 0.4$   
H<sub>2</sub>O: C, 51.52; H, 5.22; N, 12.88. Found: C, 51.70; H,  
20 5.25; N, 12.53.

#### Example 30

1,2,3,6-Tetrahydro-1-{N-[3-(4-(4-fluorobenzoyl)  
piperidin-1-yl)ethyl]}carboxamido-5-methoxycarbonyl-4  
25 -methyl-6-(3,4-difluorophenyl)-2-oxopyrimidine  
hydrochloride

a) 6-(3,4-Difluorophenyl)-1,2,3,6-tetrahydro-2-oxo-5-  
methoxycarbonyl-4-methyl-1-(4-nitrophenoxy)  
30 carbonylpyrimidine.

A well stirred solution of 6-(3,4-difluorophenyl)-1,6-  
dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-1-(4-  
nitrophenoxy)carbonylpyrimidine (10 g) in THF (200 mL)  
35 at room temperature, aqueous 6N hydrochloric acid (10  
mL) was added and the stirring was continued for 3 h.  
Solvent was evaporated and the residue was dried under

vacuum to obtain the product as a white powder (9.7 g, 100%); m.p. 185-186 °C.

5       b) 6-(3,4-Difluorophenyl)-1,2,3,6-tetrahydro-2-oxo-5-methoxycarbonyl-4-methyl-1-(2-bromoethylamino carbonyl)pyrimidine.

10       A mixture of 6-(3,4-difluorophenyl)-1,2,3,6-tetrahydro-2-oxo-5-methoxycarbonyl-4-methyl-1-(4-nitrophenoxy) carbonylpyrimidine (0.5 g, 1.118 mmol), 2-bromoethylamine hydrobromide (0.458 g, 2.237 mmol), and potassium carbonate (2.0 g) in THF/water (50 mL/5 mL) were stirred at room temperature for 1h. Then most of the solvent was evaporated at reduced pressure. The residue was partitioned between dichloromethane and water (100 mL and 100 mL). The dichloromethane layer was separated, washed with ice-cold 0.5 N NaOH (2 X 50 mL) and dried (sodium sulfate). Evaporation of the solvent gave the product as a single product (0.48 g, 100%) as a white powder; m.p. 159-160 °C.

25       c) 1,2,3,6-Tetrahydro-1-{N-[2-(4-(4-fluorobenzoyl)piperidin-1-yl)ethyl]}carboxamido-5-methoxycarbonyl-4-methyl-6-(3,4-difluorophenyl)-2-oxopyrimidine hydrochloride

30       A mixture of 6-(3,4-difluorophenyl)-1,2,3,6-tetrahydro-2-oxo-5-methoxycarbonyl-4-methyl-1-(2-bromoethylamino carbonyl)pyrimidine (43 mg, 0.1 mmol), 4-(4-fluorobenzoyl)piperidine p-toluene sulfonate (57 mg, 0.15 mmol), potassium carbonate (300 mg), and potassium iodide (30 mg) in THF(10 mL) was stirred at room temperature for 20 h. The solid material was removed by filtration, the solvent from the filtrate was evaporated, and the residue was purified by preparative thin layer chromatography on silica gel using chloroform-methanol-2M ammonia in methanol (100/2/1) as the eluent to afford the product as a viscous oil which

was converted to the HCl salt by treatment with 1N HCl in ether; m.p. 159-160 °C; Anal. Calcd. for  $C_{29}H_{29}N_4O_5F_3 \cdot 1HCl \cdot 0.8Et_2O$ : C, 57.27; H, 5.85; N, 8.56. Found: C, 57.31; H, 5.75; N, 8.79.

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#### Example 31

1,2,3,6-Tetrahydro-1-{N-[3-(4-(4-fluorophenyl)-4-hydroxypiperidin-1-yl)propyl]}carboxamido-5-methoxycarbonyl-4-methyl-6-(3,4-difluorophenyl)-2-oxopyrimidine hydrochloride

10

a) 6-(3,4-Difluorophenyl)-1,2,3,6-tetrahydro-2-oxo-5-methoxycarbonyl-4-methyl-1-(3-bromopropylamino carbonyl)pyrimidine.

15

A mixture of 6-(3,4-difluorophenyl)-1,2,3,6-tetrahydro-2-oxo-5-methoxycarbonyl-4-methyl-1-(4-nitrophenoxy) carbonylpyrimidine (1.0 g, 2.237 mmol), 3-bromopropylamine hydrobromide (0.979 g, 4.474 mmol), and potassium carbonate (4.0 g) in THF/water (100 mL/10 mL) were stirred at room temperature for 1h. Then most of the solvent was evaporated at reduced pressure. The residue was partitioned between dichloromethane and water (100 mL and 100 mL). The dichloromethane layer was separated, washed with ice-cold 0.5 N NaOH (2 X 50 mL) and dried (sodium sulfate). Evaporation of the solvent gave the product as a single product (0.98 g, 100%) as a white powder and confirmed by  $^1H$ -NMR.

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b) 1,2,3,6-Tetrahydro-1-{N-[3-(4-(4-fluorophenyl)-4-hydroxypiperidin-1-yl)propyl]}carboxamido-5-methoxycarbonyl-4-methyl-6-(3,4-difluorophenyl)-2-oxopyrimidine hydrochloride

35

A mixture of 6-(3,4-difluorophenyl)-1,2,3,6-tetrahydro-2-oxo-5-methoxycarbonyl-4-methyl-1-(3-bromopropylamino carbonyl)pyrimidine (44.6 mg, 0.1 mmol), 4-(4-fluorophenyl)-4-hydroxypiperidine (28.7 mg, 0.15 mmol), potassium carbonate (300 mg), and potassium iodide (30 mg) in THF (10 mL) was stirred at room temperature for 20 h. The solid material were removed by filtration,

the solvent from the filtrate was evaporated, and the residue was purified by preparative thin layer chromatography on silica gel using chloroform-methanol-2M ammonia in methanol (100/2/1) as the eluent to afford the product as a viscous oil which was converted to the HCl salt by treatment with 1N HCl in ether; m.p. 160-164 °C; Anal. Calcd. for  $C_{29}H_{29}N_4O_5F_3 \cdot 1HCl \cdot 0.8Et_2O$ : C, 57.27; H, 5.85; N, 8.56. Found: C, 57.31; H, 5.75; N, 8.79.

### Example 32

a) (-)-5-(Benzyloxycarbonyl)-4-ethyl-1,6-dihydro-2-methoxy-6-(3,4-difluorophenyl)-1-methoxycarbonylpyrimidine.

To a well stirred solution of (-)-5-(benzyloxycarbonyl)-1,6-dihydro-2-methoxy-4-ethyl-6-(3,4-difluorophenyl)pyrimidine (0.6 g, 1.5 mmol) and 4-(N,N-dimethylamino)pyridine (0.32 g, 2.66 mmol) in  $CH_2Cl_2$  (6 mL) was added methyl chloroformate (0.2 mL, 2.66 mmol) at room temperature. The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel with 3:1 Petroleum ether/EtOAc as the eluting system to obtain 0.45 g (78% yield) of (-)-5-(benzyloxycarbonyl)-4-ethyl-1,6-dihydro-2-methoxy-6-(3,4-difluorophenyl)-1-[methoxycarbonyl]pyrimidine as a colorless oil.

b) (-)-1,2,3,6-Tetrahydro-4-ethyl-2-oxo-6-(3,4-difluorophenyl)-1-[methoxycarbonyl]pyrimidine-5-carboxylic acid.

To a solution of (-)-5-(benzyloxycarbonyl)-4-ethyl-1,6-dihydro-2-methoxy-6-(3,4-difluorophenyl)-1-[methoxycarbonyl]pyrimidine (0.45 g, 1.18 mmol) in 20 mL of MeOH was added 0.05 g of 10% Pd on carbon and the resulting suspension was hydrogenated under 100 psi for 12 h. The catalyst was then filtered through a pad of celite and was washed thoroughly with MeOH. All the



MeOH washings were collected and the solvent was removed in vacuo to obtain 0.42 g (99% yield) of (-)-1,2,3,6-tetrahydro-4-ethyl-2-oxo-6-(3,4-difluorophenyl)-1-[methoxycarbonyl]pyrimidine-5-carboxylic acid as a white solid which was used in the next reaction without further purification.

c) (-)-1,2,3,6-Tetrahydro-5-{N-[3-(4-methoxycarbonyl)-4-phenyl-piperidin-1-yl]propyl}-carboxamido-1-methoxycarbonyl-4-ethyl-6-(3,4-difluorophenyl)-2-oxo-pyrimidine.

To a solution of (-)-1,2,3,6-tetrahydro-4-ethyl-2-oxo-6-(3,4-difluorophenyl)-1-[methoxycarbonyl]pyrimidine-5-carboxylic acid (1.18 mmol, 0.4 g) and 3-[4-methoxycarbonyl-4-phenylpiperidin-1-yl]propylamine (1.23 mmol, 0.34 g) in 20 mL  $\text{CH}_2\text{Cl}_2$  was added 4-(N,N-dimethylamino)-pyridine (1.16 mmol, 0.15 g), followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (1.84 mmol, 0.54 g) and the resulting solution was stirred at room temperature under argon for 2 days. The solution was then transferred into a separatory funnel, extracted with  $\text{CH}_2\text{Cl}_2$ , washed with sat.  $\text{NH}_4\text{Cl}$  solution (2 X 20 mL) and then with brine (20 mL). The organic layer was separated and dried over  $\text{Na}_2\text{SO}_4$ , filtered and the solvent was evaporated in vacuo to obtain an off-white solid. It was purified by column chromatography on silica gel with 10% MeOH in EtOAc as the solvent system to obtain (-)-1,2,3,6-tetrahydro-5-{N-[3-(4-methoxycarbonyl)-4-phenyl-piperidin-1-yl]propyl}-carboxamido-1-methoxycarbonyl-4-ethyl-6-(3,4-difluorophenyl)-2-oxo-pyrimidine as a white solid (0.55 g, 79% yield). M.P. 53-55°C;  $[\alpha]_D = -48.5$  (c = 0.43,  $\text{CHCl}_3$ ). It was characterized as HCl salt. Anal. Calcd. For  $\text{C}_{31}\text{H}_{37}\text{N}_4\text{O}_6\text{F}_2\text{Cl} \cdot 0.4 \text{ CHCl}_3$ : C, 55.23; H, 5.52; N, 8.20. Found: C, 55.29; H, 5.35; N, 7.99.

### Example 33

(+)-1-3-{[4-(3,4-Difluorophenyl)-2,5-dioxo-1,2,5,7-tetrahydro-4H-furo[3,4-d]pyrimidine-3-carbonyl]amino}-propyl-4-phenyl-piperidine-5-carboxylic acid methyl ester.

- 5      a)      (+)-6-(3,4-Difluorophenyl)-1,6-dihydro-2-oxo-5-methoxy-carbonyl-4-bromomethyl-1-[(4-nitrophenyloxy)carbonyl]pyrimidine.

To a well stirred solution of (+)-6-(3,4-difluorophenyl)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-1-[(4-nitrophenyloxy)carbonyl]pyrimidine (1.5 mmol, 0.66 g) in 5 mL of  
10 chloroform was added a solution of bromine (1.5 mmol, 0.09 mL) in 3 mL of chloroform at 0°C and the solution was allowed to attain room temperature over 1.5 h. The  
15 solvent was removed in vacuo and the residue was again dissolved in CHCl<sub>3</sub> (20 mL) and washed with brine. The organic layer was separated, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and the solvent was removed in vacuo to get 0.81 g of  
20 (+)-6-(3,4-difluorophenyl)-1,2,3,6-tetrahydro-2-oxo-5-methoxycarbonyl-4-bromomethyl-1-[(4-nitrophenyloxy)carbonyl]pyrimidine as a yellow foam. It was used in the next step without any purification.

- 25      b) (+)-4-(3,4-Difluorophenyl)-2,5-dioxo-1,2,4,5,6,7-hexahydro-cyclopentapyrimidine-3-carboxylic acid-4-nitrophenyl ester.

(+)-6-(3,4-Difluorophenyl)-1,6-dihydro-2-oxo-5-methoxy-carbonyl-4-bromomethyl-1-[(4-nitrophenyloxy)carbonyl]pyrimidine (1.5 mmol, 0.81 g) was heated in  
30 oil bath for 3 h (bath temperature 130°C). The brown residue thus obtained was washed with CHCl<sub>3</sub> and (+)-4-(3,4-difluoro-phenyl)-2,5-dioxo-1,2,4,5,6,7-hexahydro-cyclopenta pyrimidine-3-carboxylic acid-4-nitrophenyl ester was obtained as a pale brown solid which was used  
35 in the next step without further purification (crude wt. 0.51 g).

c) (+)-1-3-{[4-(3,4-Difluorophenyl)-2,5-dioxo-1,2,5,7-tetrahydro-4H-furo[3,4-d]-pyrimidine-3-carbonyl]amino}-propyl-4-phenyl-piperidine-5-carboxylic acid methyl ester.

5 A solution of (+)-4-(3,4-difluorophenyl)-2,5-dioxo-1,2,4,5,6,7-hexahydro-cyclopenta pyrimidine-3-carboxylic acid-4-nitrophenyl ester ((0.30 mmol, 0.13 g) and 3-[4-methoxycarbonyl-4-phenylpiperidin-1-yl]propylamine (0.32 mmol, 0.09 g) in 10 mL of  
10 anhydrous THF was stirred overnight at room temperature. The solvent was removed in vacuo and the residue was purified by column chromatography (CH<sub>2</sub>Cl<sub>2</sub> followed by 9:1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH) to obtain (+)-1-3-{[4-(3,4-difluorophenyl)-2,5-dioxo-1,2,5,7-tetrahydro-4H-furo[3,4-d]-pyrimidine-3-carbonyl]amino}-propyl-4-phenyl-piperidine-5-carboxylic acid methyl ester as a  
15 pale yellow solid (0.12 g, 70%).  $[\alpha]_D = 128.1$  (c = 0.525, CHCl<sub>3</sub>). It was characterized as HCl salt. M.P. 142-145°C; Anal. Calcd. For C<sub>29</sub>H<sub>31</sub>N<sub>4</sub>O<sub>6</sub>F<sub>2</sub>Cl.0.23 CHCl<sub>3</sub>: C, 55.55; H, 4.98; N, 8.87. Found: C, 55.25; H, 5.03; N, 8.52.  
20

#### Example 34

(-)-1-3-{[4-(3,4-Difluorophenyl)-2,5-dioxo-1,2,5,7-tetrahydro-4H-furo[3,4-d]-pyrimidine-3-carbonyl]amino}-  
25 propyl-4-phenyl-piperidine-5-carboxylic acid methyl ester. In a similar way, (-)-1-3-{[4-(3,4-difluorophenyl)-2,5-dioxo-1,2,5,7-tetrahydro-4H-furo[3,4-d]-pyrimidine-3-carbonyl]amino}-propyl-4-phenyl-piperidine-5-carboxylic acid methyl ester was  
30 prepared starting with (-)-6-(3,4-difluorophenyl)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-1-[(4-nitrophenyloxy)carbonyl]pyrimidine (overall yield 27%). M.P. 162-165 °C.  $[\alpha]_D = -121.3$  (c = 0.52, CHCl<sub>3</sub>).  
35

#### Example 35

(+)-1,2,3,6-Tetrahydro-1-{N-[4-(2-

**carboxamidophenyl)piperazin-1-yl]propyl}-carboxamido-4-methyl-6-(3,4-difluorophenyl)-2-oxo-pyrimidine**

**a) 1-(2-Carboxamidophenyl)piperazine**

5 Concentrated sulfuric acid (15 mL) was added to 1-(2-cyanophenyl)piperazine (1.5 g, 8.0 mmol) placed in a round bottom flask and the resulting slurry was stirred at room temperature for 48 h. The reaction mixture was poured on crushed ice very slowly and then basified (pH  
10 9) with 50% solution of NaOH. The aqueous layer was extracted several times with EtOAc, dried over K<sub>2</sub>CO<sub>3</sub>, filtered and the solvent was evaporated. 1-(2-carboxamidophenyl)piperazine was obtained as an off-white solid (1.2 g, 73%). It was used in the next step  
15 without further purification. Mass spectrum 206 (M + 1, 100%); Combustion analysis was obtained on its hydrochloride salt. Anal. Calcd. for C<sub>11</sub>H<sub>17</sub>N<sub>3</sub>OCl.0.3 CHCl<sub>3</sub>: C, 43.23; H, 5.55; N, 13.30. Found: C, 43.58; H, 5.70; N, 12.79.

20

**b) (+) - 1, 2, 3, 6 - Tetrahydro - 1 - { N - [ 4 - ( 2 - carboxamidophenyl)piperazin-1-yl]propyl}-carboxamido-4-methyl-6-(3,4-difluorophenyl)-2-oxo-pyrimidine.**

To a solution of (+)-6-(3,4-difluorophenyl)-1,2,3,6-tetrahydro-2-oxo-5-methoxycarbonyl-4-methyl-1-(3-bromopropylaminocarbonyl)pyrimidine (0.435 g, 1.0 mmol)  
25 and 1-(2-carboxamidophenyl)piperazine (0.4 g, 2.0 mmol) in 25 mL of anhydrous acetone was added powdered K<sub>2</sub>CO<sub>3</sub> (0.69 g, 5.0 mmol) and KI (0.17 g, 1.0 mmol) and the resulting suspension was heated to reflux for 10 h.  
30 TLC indicated complete formation of the product (R<sub>f</sub> = 0.4, 3:0.5 EtOAc/MeOH). The solvent was evaporated and the residue was dissolved in water (10 mL). The aqueous layer was extracted in EtOAc (3 X 30 mL), the separated organic extract was dried over Na<sub>2</sub>SO<sub>4</sub> and the  
35 solvent was removed in vacuo. The residue thus obtained was purified by column chromatography on

silica gel with EtOAc/MeOH (5:1) as the eluting system. (+)-1,2,3,6-tetrahydro-1-{N-[4-(2-carboxamido phenyl)piperazin-1yl]propyl}-carboxamido-4-methyl-6-(3,4-difluorophenyl)-2-oxo-pyrimidine was obtained as light yellow powder (0.48 g, 84% yield). The product was analyzed as its dihydrochloride salt. M.P. 190-193 °C;  $[\alpha]_D = 98.8$  (c = 0.31, MeOH); Anal calcd. for  $C_{29}H_{34}N_6F_2O_5Cl_2 \cdot 0.35$  EtOAc: C, 52.16; H, 5.50; N, 12.46. Found: C, 51.84; H, 5.67; N, 12.05.

#### Example 36

**1,2,3,6-Tetrahydro-1{N-[4-(N-benzimidazolyl)-piperidin-1-yl]propyl}-carboxamido-4-methyl-6-(3,4-difluorophenyl)-2-oxo-pyrimidine.**

To a solution of 6-(3,4-difluorophenyl)-1,2,3,6-tetrahydro-2-oxo-5-methoxycarbonyl-4-methyl-1-(3-bromopropylaminocarbonyl)pyrimidine (43 mg, 0.1 mmol) in 10 mL of anhydrous acetone was added 4-(N-benzimidazolyl)-piperidine (32.6 mg, 0.15 mmol) followed by  $NaHCO_3$  (41 mg, 0.3 mmol) and KI (16 mg, 0.1 mmol). The resulting suspension was heated to reflux for 10 h and then cooled to room temperature. The solvent was removed in vacuo and the residue was purified by flash column chromatography on silica gel with EtOAc followed by 10% MeOH in EtOAc to obtain 1,2,3,6-tetrahydro-1{N-[4-(N-benzimidazolyl)-piperidin-1-yl]propyl}-carboxamido-4-methyl-6-(3,4-difluorophenyl)-2-oxo-pyrimidine as an oil (15 mg, 26% yield). The product thus obtained was then dissolved in 2 mL of chloroform and 0.5 mL of HCl in  $Et_2O$  (1 M) was added at room temperature. The solvent was removed in vacuo and the HCl salt was characterized by combustion analysis. M.P. 168-172 °C. Anal calcd. for  $C_{29}H_{33}N_6F_2O_5Cl \cdot 0.75$   $CHCl_3$ : C, 50.43; H, 4.90; N, 11.86. Found: C, 50.84; H, 5.44; N, 11.46.

#### Example 37

**(-)-6-(Benzo[1,2,5]oxadiazol-5-yl)-1-carboxamido-4-et**

hyl-5-{N-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)  
propyl]}carboxamido-2-oxo-1,2,3,6-tetrahydro  
pyrimidine.

**a) 5-Methylbenzfuroxan.**

5 4-Methyl-2-nitroaniline (100 g, 0.650 mol) was  
suspended in saturated alcoholic sodium hydroxide  
solution (1.50 l). To this suspension was added with  
cooling (5 °C) commercial aqueous sodium hypochlorite  
10 until the red color disappeared. The fluffy yellow  
precipitate formed was filtered, washed with cold water  
and recrystallized from ethanol to get 5-  
methylbenzfuroxan (88.2 g, 89 % yield) as a pale solid.

**b) 5-Methylbenzofurazan.**

15 To 5-methylbenzfuroxan (88.2 g, 0.59 mol) in refluxing  
EtOH (75 ml) was added dropwise P(OEt)<sub>3</sub> (150 ml). When  
addition was complete, refluxing was continued for 1  
more hour. The solvent was removed by rotary  
20 evaporation and the residue shaken with water (200 ml)  
and allowed to stand overnight at (0-5°C). The brown  
solid so obtained was filtered, washed with water and  
chromatographed on silica gel to yield 5-  
methylbenzofurazan (70 g, 87 %) as white needles.

**c) 5-Dibromomethylbenzofurazan.**

25 5-Methylbenzofurazan (70 g, 0.52 mol), NBS (325 g), and  
benzoyl peroxide (0.5 g) were refluxed with stirring in  
carbon tetrachloride (1.5 l) with exclusion of moisture  
for 2 days. The reaction mixture was washed with water  
30 (2 X 0.5 l), brine, dried (Na<sub>2</sub>SO<sub>4</sub>), and the solvent  
removed in vacuo. The residue was chromatographed on  
silica (hexane/ EtOAc = 150/1) to get 122 g (80%) of  
the title compound as a pink solid. 5-  
Tribromomethylbenzofurazan (17 g, 9%) was also isolated  
35 as a pink solid.

**d) 5-Formylbenzofurazan.**

To a refluxing mixture of 5-dibromo methylbenzofurazan (122 g, 418 mmol) in EtOH (1 l) was added AgNO<sub>3</sub> (163 g) in 2 l of water. When addition was complete, refluxing was continued for 2 hours. The mixture was cooled and the AgBr formed was removed by filtration. The resulting solution was concentrated to a small volume and extracted with toluene (10 X 300 ml). The extract was concentrated and the residue collected was chromatographed on silica gel (3 kg), (EtOAc / hexane = 8/1000) to get the title compound (48.2 g, 78%) as a white solid.

**e) 2-Cyanoethyl 3-benzo[1,2,5]oxadiazol-5-yl-2-propionyl-acrylate.**

A mixture of 5-formylbenzofurazan (25.0 g, 168.8 mmol), 2-cyanoethyl 3-oxo-pentanoate (31.4 g, 203 mmol), and piperidinium acetate (1.22 g, 8.40 mmol) in benzene (1.5 l) was refluxed with a Dean-Stark trap for 24 hours. Benzene was evaporated, and the residue was chromatographed on silica (200 g) (EtOAc / CHCl<sub>3</sub> = 5 / 100) to get the title compound (32.36, 62.1 % yield) as a orange oil.

**f) 2-Cyanoethyl 6-benzo[1,2,5]oxadiazol-5-yl-4-ethyl-2-methoxy-1,6-dihydropyrimidine-5-carboxylate.**

A mixture of 2-cyano-ethyl 3-benzo[1,2,5]oxadiazol-5-yl-2-propionyl-acrylate (19 g, 63.48 mmol), O-methylisourea hydrogen sulfate (15.3 g, 88.9 mmol), and 4-dimethylaminopyridine (21.3 g, 175 mmol) in THF (200 ml) was stirred at 65 °C for 6 hours. The solvent was evaporated and the residue was chromatographed on silica gel (~300 g) (hexane / EtOAc = 2 / 1) to get 8 g of the title compound as an orange oily solid. This reaction was repeated for many times and the yields were between 5% and 38%.

**g) 6-Benzo[1,2,5]oxadiazol-5-yl-4-ethyl-2-methoxy-6H-**

pyrimidine-1,5-dicarboxylic acid 5-(2-cyano-ethyl) ester  
1-(4-nitro-phenyl) ester.

To a solution of 2-cyanoethyl 6-benzo  
[1,2,5]oxadiazol-5-yl-4-ethyl-2-methoxy-1,6-  
5 dihydropyrimidine-5-carboxylate (3.62 g, 10.19 mmol)  
and 4-dimethylaminopyridine (1.49 g, 12.2 mmol) in  
CH<sub>2</sub>Cl<sub>2</sub> (75 ml), at 0 °C, was added 4-  
nitrophenylchloroformate (2.46 g, 12.22 mmol). The  
10 reaction mixture was slowly warmed to r.t. at which it  
was stirred for 20 hours. Then, the solvent was  
evaporated and the residue was purified by flash column  
chromatography (~60 g of SiO<sub>2</sub>, CHCl<sub>3</sub> / EtOAc = 100 / 3)  
to get the title compound (1.96 g, 37 % yield) as a  
yellow solid.

15 h) 2-Cyanoethyl ester 6-benzo[1,2,5]oxadiazol-5-yl-4-  
ethyl-2-methoxy-1-(1-phenyl- ethyl carbamoyl)-1,6-  
dihydro-pyrimidine-5-carboxylate.

A solution of 6-benzo[1,2,5]oxadiazol-5-yl-4-ethyl-2-  
20 methoxy-6H-pyrimidine-1,5-dicarboxylic acid 5-(2-  
cyanoethyl) ester 1-(4-nitrophenyl) ester ( 2.2 g, 4.22  
mmol ) and (R)-(+)- $\alpha$ - methylbenzylamine (1.36 ml, 10.6  
mmol) in CH<sub>2</sub>Cl<sub>2</sub> (30 ml) was stirred at room temperature  
for 10 hours. The solvent was evaporated, and the  
25 residue was chromatographed on silica gel (100 g) (CHCl<sub>3</sub>  
/ EtOAc = 30 / 1) to get the two diastereomers of the  
title compound (1.03 g in total, 49%).

30 i) (-)-2-Cyanoethyl 6-benzo[1,2,5]oxadiazol-5-yl-4-  
ethyl-2-methoxy-1,6-dihydropyrimidine-5-carboxylate.

A mixture of (-)-2-cyanoethyl ester 6-  
benzo[1,2,5]oxadiazol-5-yl-4-ethyl-2-methoxy-1-(1-  
phenyl- ethyl carbamoyl)-1,6-dihydro-pyrimidine-5-  
carboxylate (557 mg, 1.11 mmol) and 1,8-  
35 diazabicyclo[5,4,0]undec-7-ene (82.5 ml, 0.55 mmol) in  
benzene (15 ml) was stirred at 50 °C for 1 hour. The  
solvent was evaporated, and the residue was



chromatographed on silica gel (~30 g) (CHCl<sub>3</sub> / EtOAc / 2 N NH<sub>3</sub> in MeOH = 40 / 10 / 1) to get the title compound (270 mg, 68.5 % yield) as a yellow solid. No rotation was observed for this compound.

5

j) (-)-6-Benzo[1,2,5]oxadiazol-5-yl-4-ethyl-2-methoxy-6H-pyrimidine-1,5-dicarboxylic acid 5-(2-cyanoethyl) ester 1-(4-nitro-phenyl) ester.

To a solution of (-)-2-cyanoethyl 6-benzo[1,2,5]oxadiazol-5-yl-4-ethyl-2-methoxy-1,6-dihydropyrimidine-5-carboxylate (220 mg, 0.62 mmol) and 4-dimethylaminopyridine (99 mg, 0.81 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (12 ml), at 0 °C, was added 4-nitrophenylchloroformate (164 mg, 0.81 mmol). The reaction mixture was slowly warmed to r.t. at which it was stirred for 24 hours. The solvent was evaporated and the residue was purified by flash column chromatography (~30 g of SiO<sub>2</sub>, CHCl<sub>3</sub> / EtOAc = 38/1) to get the title compound (301 mg, 93 % yield) as a yellow solid.

20

k) (-)-6-(Benzo[1,2,5]oxadiazol-5-yl)-1-carboxamido-4-ethyl-5-{N-[3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propyl]}carboxamido-2-oxo-1,6-dihydropyrimidine.

To (-)-6-benzo[1,2,5]oxadiazol-5-yl-4-ethyl-2-methoxy-6H-pyrimidine-1,5-dicarboxylic acid 5-(2-cyanoethyl) ester 1-(4-nitrophenyl) ester (100 mg, 0.19 mmol) in dry THF (10 ml) ammonia (gas) was introduced with a balloon at room temperature. It was stirred at room temperature for 14 hours. TLC and <sup>1</sup>H NMR of the reaction mixture showed that the reaction was complete. NaOH (1 N, 3 ml) was added at room temperature. After it was stirred for 6 hours, HCl solution (6 N, 4 ml) was added. It was stirred at room temperature for 14 hours. The solvent was evaporated to get a white solid which was used directly in the next step.

35

A mixture of the crude product from the above step, 4-dimethyl aminopyridine (61mg, 0.5 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (96 mg, 0.5 mmol) in  $\text{CH}_2\text{Cl}_2$  (15 ml) was stirred at room temperature for 4 hours. Methyl 1-(3-amino-propyl)-4-phenyl-piperidine-4-carboxylate (140 mg, 0.5 mmol) was added. The reaction mixture was stirred at room temperature for 16 hours. The solvent was evaporated and the residue was chromatographed on silica gel (5 g) ( $\text{CHCl}_3$  / MeOH / 2 N  $\text{NH}_3$  in MeH = 250 / 2 / 1) to get the title compound as a white solid (10.8 mg, 10 % yield over 3 steps).  $[\alpha]_D = -303.9$ . Hydrochloride of the title compound was made with HCl in ether. M.P. of the salt: 140-143 °C. Calculated for  $\text{C}_{30}\text{H}_{35}\text{N}_7\text{O}_6 + 1.0\text{HCl} + 0.6$  ether: C, 58.03 %; H, 6.31 %; N, 14.62 %. Found: C, 58.07 %; H, 6.08 %; N, 14.66 %.

#### Example 38

6-(3,4-Difluoro-phenyl)-1-[3-(3',6'-dihydro-[2,4']bipyridinyl-1'-yl)-propylcarbamoyl]-4-methyl-5-methoxycarbonyl-2-oxo-1,2,3,6-tetrahydropyrimidine hydrochloride.

a) 1-(3-Aminopropyl)-4-[pyrid-2-yl]pyridinium bromide hydrobromide.

A solution of 2,4'-dipyridyl (5.0 g, 32.0 mmol) and 3-bromopropylamine hydrobromide (7.0 g, 32.0 mmol) in DMF (50.0 mL) and acetonitrile (50.0 mL) was heated at 90-95°C for 1 h. After cooling, the white solid that came out was filtered, washed with  $\text{Et}_2\text{O}$  and dried. The mother liquor was concentrated to remove  $\text{Et}_2\text{O}$  and then heated to 90-95°C for 4 h. The solvent was evaporated and the white residue was triturated with  $\text{Et}_2\text{O}$  (100.0 mL) and filtered. The combined weight of the salt was 11.6 g (97%).

b) 3-(3',6'-Dihydro-2'-H-[2,4']bipyridinyl-1'-yl)-propylamine.

To a solution of 1-(3-aminopropyl)-4-[pyrid-2-yl]pyridinium bromide hydrobromide (0.66 g, 1.75 mmol) in 20.0 mL MeOH was added NaBH<sub>4</sub> (0.101 g, 2.62 mmol) in small portions. The reaction mixture was stirred for 30 min and then quenched with 6M HCl solution. The solution was concentrated to 20.0 mL and basified with 50% NaOH solution to pH 12. Extracted with CHCl<sub>3</sub> (5 x 30.0 mL), dried over MgSO<sub>4</sub> and the solvent was removed to give 3-(3',6'-dihydro-2'-H-[2,4']bipyridinyl-1'-yl)-propylamine as an oil (0.37 g, 96% yield). It is used in the next step immediately without purification.

**c) 6-(3,4-Difluoro-phenyl)-1-[3-(3',6'-dihydro-[2,4']bipyridinyl-1'-yl)-propylcarbamoyl]-4-methyl-5-methoxycarbonyl-2-oxo-1,2,3,6-tetrahydro-pyrimidine hydrochloride.**

A solution of 6-(3,4-difluorophenyl)-4-methyl-5-methoxycarbonyl-1-(4-nitrophenoxy)carbonyl-2-oxo-1,2,3,6-tetrahydro-pyrimidine (20 mg, 0.045 mmol) and 3-(3',6'-dihydro-2'-H-[2,4']bipyridyl-1-yl)propylamine (9.7 mg, 0.045 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 ml) was stirred at room temperature for 3 days. The solvent was removed in vacuum. The residue was separated on preparative TLC (CHCl<sub>3</sub> / MeOH = 100 / 15) to get the title compound (21mg, 89 % yield) as a yellow solid. Hydrochloride salt was made with HCl in ether. M.P. of the salt: 242-244°C. Calcd for C<sub>27</sub>H<sub>29</sub>N<sub>5</sub>O<sub>4</sub>F<sub>2</sub> + 2.0 HCl + 1.05 CHCl<sub>3</sub> + 1.05 ether: C, 48.32 %; H, 5.35 %; N, 8.74 %. Found: C, 48.10 %; H, 5.13 %; N, 8.72 %.

#### Example 39

**6-(3,4-Difluorophenyl)-1-(3-imidazol-1-yl-propylcarbamoyl)-4-methyl-2-oxo-1,2,3,6-tetrahydro-pyrimidine-5-carboxylic acid methyl ester.**

A solution of 6-(3,4-difluorophenyl)-4-methyl-5-methoxycarbonyl-1-(4-nitrophenoxy)carbonyl-2-oxo-

1,2,3,6-tetrahydro-pyrimidine (100 mg, 0.22 mmol) and 1-(3-aminopropyl)imidazole (40 ml, 0.34 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 ml) was stirred at room temperature for 3 hours. The solvent was removed in vacuum. The residue was separated on preparative TLC ( $\text{CHCl}_3$  / MeOH = 100 / 15) to get the title compound (80 mg, 84 % yield) as a white solid. Hydrochloride of title compound was made with HCl in ether. Calcd for  $\text{C}_{20}\text{H}_{21}\text{N}_5\text{O}_4\text{F}_2 + 0.3 \text{ H}_2\text{O}$ : C, 54.74 %; H, 4.99 %; N, 15.89 %. Found: C, 54.92 %; H, 4.65 %; N, 15.77 %. M.P. of the salt: 221-224°C.

**E x a m p l e 4 0**

**6-(3,4-Difluorophenyl)-1-{N-[3-(2-phenylimidazol-1-yl)propyl]}carboxamido-4-methyl-5-methoxycarbonyl-2-oxo-1,2,3,6-tetrahydropyrimidine hydrochloride.**

A mixture of 6-(3,4-difluorophenyl)-1,2,3,6-tetrahydro-2-oxo-5-methoxycarbonyl-4-methyl-1-(3-bromopropylamino carbonyl)pyrimidine (100 mg, 0.22 mmol), 2-phenylimidazole (32.3 mg, 0.22 mmol), and  $\text{CsCO}_3$  (358 mg, 1.1 mmol) in DMF (10 ml) was stirred at room temperature for 2 days. The solid was filtered out. The solution was concentrated and separated on preparative TLC (EtOAc / hexane = 3 / 1) to get the title compound (41 mg, 37 % yield) as a white oily solid. Hydrochloride of title compound was made with HCl in ether. M.P. of the salt: 278-282 °C. Calculated for  $\text{C}_{26}\text{H}_{25}\text{N}_5\text{O}_4\text{F}_2 + 2.0 \text{ HCl} + 0.25 \text{ H}_2\text{O}$ : C, 52.23 %; H, 4.60 %; N, 11.60 %. Found: C, 52.21 %; H, 4.69 %; N, 11.11 %.

**Example 41 and Example 42**

**(+)-, and (-)-3,6-Dihydro-1-{N-[4-(2-pyridyl)-piperidine-1-yl] propyl}carboxamido-5-methoxy carbonyl-2-oxo-6-(3,4,5-trifluorophenyl)-4-methyl pyrimidine dihydrochloride.**

**a) Methyl 2-acetyl-3-(3,4,5-trifluoro-phenyl)-acrylate.**

A mixture of 3,4,5-trifluorobenzaldehyde (1.0 g, 6.3 mmol), methyl acetoacetate (0.81 ml, 7.5 mmol), and piperidinium acetate (45 mg, 0.31 mmol) in benzene (10 ml) was refluxed with a Dean-Stark trap for 12 hours.

5 The solvent was evaporated, and the residue was chromatographed on silica gel (~50 g) (EtOAc / hexane = 1 / 6) to get the title compound (825 mg, 51 % yield) as a mixture of cis and trans isomers (yellow oil).

10 **b) Methyl 2-methoxy-4-methyl-6-(3,4,5-trifluorophenyl)-1,6-dihydro-pyrimidine-5-carboxylate.**

A mixture of methyl 2-acetyl-3-(3,4,5-trifluorophenyl)-acrylate (670 mg, 2.60 mmol), O-methylisourea hydrogen hemisulfate (448 mg, 3.63 mmol), and 4-  
15 dimethylaminopyridine (407 mg, 3.63 mmol) in ethanol (20 ml) was stirred at 65 °C for 2 days. The solid formed was filtered out. The filtrate was concentrated and chromatographed on silica gel (30 g) (CH<sub>2</sub>Cl<sub>2</sub> / EtOAc = 9 / 1) to get the title compound (390 mg, 48 % yield)  
20 as a pale yellow oil. Calculated for C<sub>14</sub>H<sub>13</sub>N<sub>2</sub>O<sub>3</sub>F<sub>3</sub>; C, 53.50 %; H, 4.20 %; N, 8.90 %. Found: C, 53.24 %; H, 4.20 %; N, 8.60 %.

25 **c) 1,6-Dihydro-5-methoxycarbonyl-2-methoxy-4-methyl-1-(4-nitro phenyloxy)carbonyl -6-(3,4,5-trifluorophenyl)-pyrimidine.**

To a solution of methyl 1,6-dihydro-2-methoxy-4-methyl-6-(3,4,5-trifluorophenyl)-pyrimidine-5-carboxylate (385 mg, 1.23 mmol) and 4-  
30 dimethylaminopyridine (195 mg, 1.60 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (15 ml), at room temperature, was added 4-nitrophenyl chloroformate (322 mg, 1.60 mmol). The reaction solution was stirred at room temperature for 2 days. The white solid formed was filtered out. The filtrate  
35 was concentrated and chromatographed on silica gel (~20 g) (CHCl<sub>3</sub> / CH<sub>3</sub>OH = 9 / 1) to get the titled compound (206 mg, 35 % yield) as a white solid. Calculated for

$C_{21}H_{16}N_3O_7F_3 + 1.0 H_2O$ : C, 50.71 %; H, 3.65 %; N, 8.45 %.  
Found: C, 50.83%; H, 3.29 %; N, 8.33 %.

5 d) 1,6-Dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-1-{N-[4-(2-pyridyl)-piperidin-1-yl]-propyl}carbamoyl-6-(3,4,5-trifluoro-phenyl)-pyrimidine.

10 A mixture of 1,6-dihydro-5-methoxycarbonyl-2-methoxy-(4-nitrophenoxy)carbonyl-6-(3,4,5-trifluorophenyl)-4-methyl-pyrimidine (25 mg, 0.05 mmol) and 3-[4-(2-pyridyl)-piperidin-1-yl]-propylamine (16 mg, 0.078 mmol) was stirred at room temperature for 12 hours. The solvent was evaporated and the residue chromatographed on silica gel (~5 g)  
15 ( $CHCl_3 / EtOAc = 30 / 1$ ) to get the title compound (16 mg, 57 % yield) as a pale solid.

20 e) 1,2,3,6-Tetrahydro-5-methoxycarbonyl-4-methyl-2-oxo-1-{N-[4-(2-pyridyl)-piperidine-1-yl]-propyl}carboxamido-6-(3,4,5-trifluorophenyl)-pyrimidine dihydrochloride.

1,6-Dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-1-{N-[4-(2-pyridyl)-piperidin-1-yl]-propyl}carbamoyl-6-(3,4,5-trifluoro-phenyl)-pyrimidine from the previous  
25 step was dissolved in  $CH_2Cl_2$  (5 ml) and concentrated HCl solution (0.5 ml) was added. The reaction mixture was stirred at room temperature for 1 hour. NaOH solution (1 N) was added to neutralized the reaction mixture. It was extracted with  $CH_2Cl_2$ . The extractant was dried  
30 ( $Na_2SO_4$ ) and concentrated to get the title compound (16 mg, quantitative) as a pale solid. Hydrochloride of the title compound was made with HCl in ether. Calculated for  $C_{27}H_{29}N_5O_4F_3 + 2.0 HCl + 4.0 THF + 0.8 CH_2Cl_2$ : C, 54.02 %; H, 6.69 %; N, 7.19 %. Found:  
35 C, 54.00 %; H, 6.48 %; N, 7.42 %.

f) (+)-, and (-)-3,6-Dihydro-1-{N-[4-(2-pyridyl)-

piperidine-1-yl] propyl}carboxamido-5-methoxy  
carbonyl-2-oxo-6-(3,4,5-trifluorophenyl)-4-methyl  
pyrimidine dihydrochloride.

5 The enantiomers were separated by chiral HPLC  
separation (column: chiralpak AS) of the racemic  
1,2,3,6-tetrahydro-1-{N-[4-(2-pyridyl)-piperidine-1-y  
l]propyl}carboxamido-5-methoxycarbonyl-2-oxo-6-(3,4,5  
-trifluorophenyl)-4-methylpyrimidine dihydrochloride  
which was synthesized in the previous step. The (+)  
10 isomer:  $[\alpha]_D = +80.4$  (c = 0.2 g in 100 ml  
dichloromethane):. The (-) isomer:  $[\alpha]_D = -82.2$ .  
Hydrochloride salts of the title compounds was made  
with HCl in ether.

15 **Example 43**

(+)-1,2,3,6-Tetrahydro-5-methoxycarbonyl-4-  
methoxymethyl-2-oxo-1-{N-[4-(2-pyridyl)-  
piperidine-1-yl]-propyl}carboxamido-  
6-(3,4,5-trifluorophenyl)-pyrimidine dihydrochloride.

20 a) Methyl 2-methoxyacetyl-3-(3,4,5-trifluoro-phenyl)-  
acrylate.

A mixture of 3,4,5-trifluoro benzaldehyde (10 g, 62.5  
mmol), methyl 4-methoxyacetoacetate (9.7 ml, 75.0  
mmol), and piperidinium acetate (450 mg, 3.1 mmol) in  
25 benzene (100 ml) was refluxed with a Dean-Stark trap  
for 8 hours. The white solid formed (some side  
product) was filtered out. The solvent was evaporated,  
and the residue was chromatographed on silica gel (~ 1  
Kg) (toluene / t-butyl methyl ether = 8 / 1) to get the  
30 title compound (4.5 g, 25% yield) as a mixture of cis  
and trans isomers (white solid).

b) 1,6-Dihydro-2-methoxy-5-methoxycarbonyl-4-  
methoxymethyl-6-(3,4,5-trifluoro-phenyl)-pyrimidine.

35 A mixture of methyl 2-methoxyacetyl-3-(3,4,5-  
trifluoro-phenyl)-acrylate (6.0 g, 20.8 mmol), O-  
methylisourea hydrogen hemisulfate (3.6 g, 29.2 mmol),

and 4-dimethylaminopyridine (3.6 g, 29.2 mmol) in ethanol (20 ml) was stirred at 65 °C for 12 hours. The solid formed was filtered out. The filtrate was concentrated and chromatographed on silica gel (~1 kg) (hexane / ether = 2 / 1) to get the title compound (4.0 g, 56 % yield) as a pale colorless oily solid.

c) **1,6-Dihydro-2-methoxy-5-methoxycarbonyl-4-methoxymethyl-1-(4-nitrophenyloxy)carbonyl-6-(3,4,5-trifluorophenyl)-pyrimidine.**

To a solution of 1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methoxymethyl-6-(3,4,5-trifluorophenyl)-pyrimidine (3.24 g, 9.41 mmol) and 4-dimethylaminopyridine (1.38 g, 11.3 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 ml), at room temperature, was added 4-nitrophenyl chloroformate (2.28 g, 11.3 mmol). The reaction solution was stirred at room temperature for 2 days. The white solid formed was filtered out. The filtrate was concentrated and chromatographed on silica gel (hexane / ether = 1 / 1) to get the title compound (3.70 g, 77 % yield) as a yellow solid.

d) (+)-, and (-)-**1,6-Dihydro-2-methoxy-5-methoxycarbonyl-4-methoxymethyl-1-[N-(2-methylbenzyl)]carbamoyl-6-(3,4,5-trifluoro-phenyl)-pyrimidine.**

A mixture of 1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methoxymethyl-1-(4-nitrophenyloxy)carbonyl-6-(3,4,5-trifluorophenyl)-pyrimidine (3.80 g, 7.46 mmol) and (R)-(+)- $\alpha$ -methylbenzylamine (2.02 mg, 16.4 mmol) in CH<sub>2</sub>Cl<sub>2</sub> was stirred at room temperature for 2 days. The solvent was evaporated and the residue chromatographed on silica gel (toluene /t-butyl methyl ether = 5 / 1) to get the title compound as yellow oil solids. For the less polar isomer (1.81 g, 50 %yield):  $[\alpha]_D = +164.3$ . For the more polar isomer (1.79 g, 50 % yield):  $[\alpha]_D = -86.2$ .



e) ( + ) -1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methoxymethyl-6-(3,4,5-trifluoro-phenyl)-pyrimidine.

A mixture of (+)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methoxymethyl-1-[N-(2-methylbenzyl)]carbamoyl-6-(3,4,5-trifluoro-phenyl)-pyrimidine (1.81 g, 3.81 mmol) and 1,8-diazabicyclo[5,4,0]undec-7-ene (0.28 ml, 1.90 mmol) in benzene (10 ml) was stirred at room temperature for 4 days. The solvent was evaporated, and the residue was chromatographed on silica gel (~500 g) (hexane / ether = 2.5 / 1) to get the title compound (1.2 g, 91 % yield) as a yellow oil. No rotation was observed for this compound.

f) (+) -1,6-Dihydro-2-methoxy-5-methoxycarbonyl-4-methoxymethyl-1-(4-nitrophenyloxy) carbonyl-6-(3,4,5-trifluorophenyl)-pyrimidine.

To a solution of 1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methoxymethyl-6-(3,4,5-trifluoro-phenyl)-pyrimidine (1.20 g, 3.49 mmol) and 4-dimethylaminopyridine (0.51 g, 4.18 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 ml), at room temperature, was added 4-nitrophenyl chloroformate (0.84 g, 11.3 mmol). The reaction solution was stirred at room temperature for 12 hours. The white solid formed was filtered out. Trials to purify the crude product on silica gel only hydrolyzed the desired product to the start materials. The crude product was used in the next step without any further purification.

g) (+) -1,6-Dihydro-2-methoxy-5-methoxycarbonyl-4-methoxymethyl-1-{N-[4-(2-pyridyl)-piperidin-1-yl]-propyl}carbamoyl-6-(3,4,5-trifluoro-phenyl)-pyrimidine.

A mixture of (+)-1,6-dihydro-2-methoxy-5-methoxy carbonyl-4-methoxymethyl-1-(4-nitrophenyloxy) carbonyl-6-(3,4,5-trifluorophenyl)-pyrimidine and 3-[4-(2-pyridyl)-piperidin-1-yl]-propylamine (215 mg,

1.05 mmol) was stirred at room temperature for 12 hours. The solvent was evaporated and the residue chromatographed on prep. TLC (CHCl<sub>3</sub> / MeOH = 100 / 15) to get the title compound (115 mg, 22 % yield over 2 steps) as a yellow oil.

h) (+)-1,2,3,6-Tetrahydro-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1-{N-[4-(2-pyridyl)-piperidine-1-yl]-propyl}carboxamido-6-(3,4,5-trifluorophenyl)-pyrimidine dihydrochloride.

1,6-Dihydro-2-methoxy-5-methoxycarbonyl-4-methoxymethyl-1-{N-[4-(2-pyridyl)-piperidin-1-yl]-propyl}carbamoyl-6-(3,4,5-trifluoro-phenyl)-pyrimidine from the previous step was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (5 ml) and HCl solution (6 N, 0.5 ml) was added. The reaction mixture was stirred at room temperature for 4 hour. KOH solution (1 N) was added to neutralize the reaction mixture. It was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The extractant was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to get the title compound (106 mg, 94 % yield) as a pale oily solid.  $[\alpha]_D = + 78.6$  (c = 0.5 g in 100 ml dichloromethane). Hydrochloride of the title compound was made with HCl in ether. Calculated for C<sub>28</sub>H<sub>32</sub>N<sub>5</sub>O<sub>5</sub>F<sub>3</sub> + 3.8 HCl + 1.8 EtOAc: C, 48.44%; H, 5.80%; N, 8.02 %. Found: C, 48.19 %; H, 5.38 %; N, 8.32%.

#### Example 44

(-)-1,2,3,6-Tetrahydro-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1-{N-[4-(2-pyridyl)-piperidine-1-yl]-propyl}carboxamido-6-(3,4,5-trifluorophenyl)-pyrimidine dihydrochloride.

a) (-)-1,6-Dihydro-2-methoxy-5-methoxycarbonyl-4-methoxymethyl-6-(3,4,5-trifluoro-phenyl)-pyrimidine.

A mixture of (-)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methoxymethyl-1-[N-(2-methylbenzyl)]carbamoyl-6-(3,4,5-trifluoro-phenyl)-

pyrimidine (1.79 g, 3.80 mmol) and 1,8-diazabicyclo[5,4,0]undec-7-ene (0.28 ml, 1.90 mmol) in benzene (10 ml) was stirred at room temperature for 4 days. The solvent was evaporated, and the residue was chromatographed on silica gel (~500 g) (hexane / ether = 2.5 / 1) to get the title compound (0.92 g, 70 %) as a yellow oil. No rotation was observed for this compound.

10      b)      (-)-1,6-Dihydro-2-methoxy-5-methoxycarbonyl-4-methoxymethyl-1-(4-nitrophenyloxy)carbonyl-6-(3,4,5-trifluorophenyl)-pyrimidine.

To a solution of 1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methoxymethyl-6-(3,4,5-trifluorophenyl)-pyrimidine (0.92 g, 2.67 mmol) and 4-dimethylaminopyridine (0.46 g, 3.74 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 ml), at room temperature, was added 4-nitrophenyl chloroformate (0.75 g, 3.74 mmol). The reaction solution was stirred at room temperature for 2 days. The white solid formed was filtered out. The filtrate was concentrated and chromatographed on silica gel (hexane / ether = 3 / 1) to get the title compound (1.01 g, 79 % yield) as a yellow solid.

25      c)      (-)-1,6-Dihydro-2-methoxy-5-methoxycarbonyl-4-methoxymethyl-1-{N-[4-(2-pyridyl)-piperidin-1-yl]-propyl}carbamoyl-6-(3,4,5-trifluorophenyl)-pyrimidine.

A mixture of (-)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methoxymethyl-1-(4-nitrophenyloxy)carbonyl-6-(3,4,5-trifluorophenyl)-pyrimidine (300 mg, 0.59 mmol) and 3-[4-(2-pyridyl)-piperidin-1-yl]-propylamine (160 mg, 0.77 mmol) was stirred at room temperature for 12 hours. The solvent was evaporated and the residue chromatographed on prep. TLC (CHCl<sub>3</sub> / MeOH / 2 N NH<sub>3</sub> in MeOH = 20 / 2 / 1) to get the title compound (290 mg, 83 % yield) as a yellow oil.

d) (-)-1,2,3,6-Tetrahydro-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1-{N-[4-(2-pyridyl)-piperidine-1-yl]-propyl}carboxamido-6-(3,4,5-trifluorophenyl)-pyrimidine dihydrochloride.

- 5 (-)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methoxymethyl-1-{N-[4-(2-pyridyl)-piperidin-1-yl]-propyl}carbamoyl-6-(3,4,5-trifluoro-phenyl)-pyrimidine (290 mg, 0.49 mmol) was dissolved in  $\text{CH}_2\text{Cl}_2$  (5 ml) and HCl solution (6 N, 2 ml) was added. The reaction
- 10 mixture was stirred at room temperature for 10 hour. KOH solution (1 N) was added to neutralized the reaction mixture. It was extracted with  $\text{CH}_2\text{Cl}_2$ . The extractant was dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated to get the title compound (180 mg, 64 % yield) as a pale oily
- 15 solid.  $[\alpha]_D = -31.4$  ( $c = 0.44$  g in 100 ml dichloromethane). Hydrochloride of the title compound was made with HCl in ether. Calculated for  $\text{C}_{28}\text{H}_{32}\text{N}_5\text{O}_5\text{F}_3 + 2.0 \text{ HCl} + 0.8 \text{ ether} + 0.8 \text{ CH}_2\text{Cl}_2$ : C, 50.59 %; H, 5.78 %; N, 9.22 %. Found: C, 50.86 %; H, 5.82 %;
- 20 N, 8.75 %.

#### Example 45

1,2,3,6-Tetrahydro-5-methoxycarbonyl-4-methyl-2-oxo-1-{N-[4-(2-pyridyl)-piperidine-1-yl]-propyl}carboxamido-6-(2,4,5-trifluorophenyl)-pyrimidine dihydrochloride.

25

a) Methyl 2-acetyl-3-(2,4,5-trifluoro-phenyl)-acrylate.

- A mixture of 2,4,5-trifluorobenzaldehyde (1.0 g, 6.3 mmol), methyl acetoacetate (0.81 ml, 7.4 mmol), and
- 30 piperidinium acetate (38 mg, 0.26 mmol) in benzene (10 ml) was stirred at room temperature for 2 days. The solvent was evaporated, and the residue was chromatographed on silica gel (~50 g) (hexane / ether = 5 / 1) to get the title compound (1.60 g,
- 35 quantitative) as a mixture of cis and trans isomers (colorless oil).

**b) 1,6-Dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-6-(2,4,5-trifluoro-phenyl)-pyrimidine.**

A mixture of methyl 2-acetyl-3-(2,4,5-trifluoro-phenyl)-acrylate (1.60 g, 6.20 mmol), O-methylisourea hydrogen hemisulfate (1.07 g, 8.68 mmol), and 4-dimethylaminopyridine (1.06 g, 8.68 mmol) in ethanol (10 ml) was stirred at 65 °C for 2 days. The solid formed was filtered out. The filtrate was concentrated and chromatographed on silica gel (~50 g) (CH<sub>2</sub>Cl<sub>2</sub> / EtOAc = 9 / 1) to get the title compound (982 mg, 50 % yield) as a pale colorless oily solid.

**c) 1,6-Dihydro-5-methoxycarbonyl-2-methoxy-4-methyl-1-(4-nitro phenyloxy)carbonyl -6-(2,4,5-trifluorophenyl)-pyrimidine.**

To a solution of 1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-6-(2,4,5-trifluoro-phenyl)-pyrimidine (600 mg, 1.91 mmol) and 4-dimethylaminopyridine (280 mg, 2.29 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (8 ml), at room temperature, was added 4-nitrophenyl chloroformate (462 mg, 2.29 mmol). The reaction solution was stirred at room temperature for 18 hours. The white solid formed was filtered out. The filtrate was concentrated and chromatographed on silica gel (~50 g) (hexane / ether = 4 / 1) to get the title compound (143 mg, 16 % yield) as a white solid.

**d) 1,6-Dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-1-{N-[4-(2-pyridyl)-piperidin-1-yl]-propyl}carbamoyl-6-(2,4,5-trifluoro-phenyl)-pyrimidine.**

A mixture of 1,6-dihydro-5-methoxycarbonyl-2-methoxy-4-methyl-1-(4-nitrophenyloxy)carbonyl-6-(2,4,5-trifluorophenyl)-pyrimidine (70 mg, 0.146 mmol) and 3-[4-(2-pyridyl)-piperidin-1-yl]propylamine (46 mg, 0.220 mmol) was stirred at room temperature for 12 hours. The solvent was evaporated and the residue separated on preparative TLC (CHCl<sub>3</sub> / MeOH / 2 N NH<sub>3</sub> in

MeOH = 20 / 2 / 1) to get the title compound (59 mg, 72 % yield ) as a yellow oil.

- 5 e) 1,2,3,6-Tetrahydro-5-methoxycarbonyl-4-methyl-2-oxo-1-{N-[4-(2-pyridyl)-piperidine-1-yl]-propyl}carboxamido-6-(2,4,5-trifluorophenyl)-pyrimidine dihydrochloride.
- 10 1,6-Dihydro-2-methoxy-5methoxycarbonyl-4-methyl-1-{N-[4-(2-pyridyl)-piperidin-1-yl]-propyl}carbamoyl-6-(2,4,5-trifluoro-phenyl)-pyrimidine (59 mg, 0.11 mmol) was dissolved in THF (3 ml) and HCl solution (6 N, 2 ml) was added. The reaction mixture was stirred at room temperature for 6 hour. KOH solution (1 N) was
- 15 added to neutralized the reaction mixture. It was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The extractant was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to get the title compound (50 mg, 87 % yield) as a white solid. Hydrochloride of the title compound was made with HCl in ether. Calculated for C<sub>27</sub>H<sub>30</sub>N<sub>5</sub>O<sub>4</sub>F<sub>2</sub> + 2.0 HCl + 1.0 C<sub>6</sub>H<sub>12</sub> + 1.0 CHCl<sub>3</sub>: C, 49.68
- 20 %; H, 5.52 %; N, 8.52 %. Found: C, 49.22 %; H, 6.11 %; N, 8.59 %. M.P. of the salt: 239-243 °C.

#### Example 46

- 25 4-(3,4-Difluorophenyl)-3-[3-(3-hydroxy-3-phenyl-8-aza bicyclo[3.2.1]oct-8-yl)propylcarbamoyl]-6-methyl-2-oxo-1,2,3,6-tetrahydro-pyrimidine-5-carboxylic acid methyl ester

- a) 8-Benzyl-3-phenyl-8-azabicyclo[3.2.1]octan-3-ol:  
N-benzyltropinone (14.4 g, 66.7 mmol) was added
- 30 dropwise (neat) to a solution of phenyl magnesium bromide (100 mL, 0.1 M in THF). The addition was continued as such a rate to maintain a gentle reflux. Once the addition was complete, the reaction mixture was heated at reflux temperature for 19 hours, cooled
- 35 to room temperature, poured over 200 mL of crushed ice, saturated with ammonium chloride, and extracted with 3 X 100 mL of ethyl acetate. The combined organic

extracts were dried ( $K_2CO_3$ ), solvent removed in Vacuo, and the crude product was chromatographed on 500 g of silica packed with  $CHCl_3$ . The column was eluted with  $CHCl_3$  (1 L), 5%EtOAc- $CHCl_3$  (1 L), 10% (1 L), 20%, (1 L), 30% (1 L), 50% (1 L), 100% EtOAc (1 L), and 10% MeOH-EtOAc (2 L), to give 11.8 g (40%) of the desired product as a slightly yellow oily solid. Anal. Calc. for  $C_{20}H_{23}N_1O_1$ : C, 81.87; H, 7.90; N, 4.77. Found: C, 81.63; H, 8.01; N, 4.70.

**b) 3-Phenyl-8-azabicyclo[3.2.1]octan-3-ol:**

A mixture of 5.10 g of 8-benzyl-3-phenyl-8-azabicyclo[3.2.1]octan-3-ol (17.4 mmol), 3.15 g of 10% Pd/C in 50 mL of 95% ethanol was hydrogenated in a pressurized bomb (200 psi) at 60-70 °C (bath temperature) for 16 hours. The reaction mixture was filtered through a pad of Celite, and the solids were washed with 5 X 30 mL of methanol. The combined organic extracts were concentrated, and the crude product was chromatographed on 300 g of silica packed with EtOAc-MeOH-isopropanol (30:2:1). The column was eluted with EtOAc-MeOH-isopropanol 25:2:1 (1 L), 20:2:1 (1 L), and 15:2:1 (1 L) to give 3.16 g (89%) of the desired product as a slightly yellow oily solid. Anal. Calc. for  $C_{13}H_{17}N_1O_1$ : C, 76.81; H, 8.43; N, 6.89. Found: C, 76.57; H, 8.53; N, 6.80.

**c) 4-(3,4-Difluorophenyl)-3-[3-(3-hydroxy-3-phenyl-8-azabicyclo[3.2.1]oct-8-yl)propylcarbamoyl]-6-methyl-2-oxo-1,2,3,6-tetrahydro-pyrimidine-5-carboxylic acid methyl ester.**

A mixture of 243 mg of 3-phenyl-8-azabicyclo[3.2.1]octan-3-ol (1.2 mmol), 640 mg of 1,2,3,6-tetrahydro-1-{3-bromopropyl}carboxamido-5-methoxycarbonyl-4-methyl-6-(3,4-difluorophenyl)-2-oxopyrimidine (1.44 mmol), 197 mg of  $K_2CO_3$  (1.44 mmol), catalytic amounts (a few crystals) of KI in 10 mL of

ethanol were heated at reflux temperature for 4 hours. The reaction mixture was cooled to room temperature, and the crude product was purified with preparative TLC (2000 microns, 10% MeOH-EtOAc) to give 290 mg (43%) of the desired product as a slightly yellow viscous oil. Anal. Calc. For  $C_{30}H_{34}F_2N_4O_5 + 1.0$  Methanol: C, 61.99; H, 6.38; N, 9.33. Found: C, 62.12; H, 6.02; N, 9.58. The hydrochloride salt was prepared by dissolving 150 mg of the free base in minimum EtOAc and excess 1N HCl in ether was added. The solvent was decanted and the separated oil was triturated with ether to give the hydrochloride as a slightly yellow powder: Anal. Calc. for  $C_{30}H_{34}F_2N_4O_5 + 1.0$  HCl +  $1.2$   $H_2O$ : C, 57.50; H, 6.01; N, 8.94. Found: C, 57.76; H, 5.82; N, 8.50.

#### Example 47 and Example 48

1,2,3,6-Tetrahydro-1-(N-(3-(3-imidazol-1-yl)propyl)amino)propylcarboxamido-5-methoxycarbonyl-2-oxo-6-(3,4-difluorophenyl)-4-methylpyrimidine dihydrochloride and 1,2,3,6-Tetrahydro-1-(N-(3-(2-indol-3-yl))ethyl)amino)propylcarboxamido-5-methoxycarbonyl-2-oxo-6-(3,4-difluorophenyl)-4-methylpyrimidine hydrochloride

In two separate reaction vessels, a mixture of 89 mg of 1,2,3,6-tetrahydro-1-{3-bromopropyl}carboxamido-5-methoxy carbonyl-4-methyl-6-(3,4-difluorophenyl)-2-oxo pyrimidine (0.200 mmol), 0.200 mmol of the following nucleophiles (25.0 mg of 1-(3-aminopropyl)imidazole, 25 mg of tryptamine), 89 mg of  $K_2CO_3$ , in 1 mL of acetonitrile were heated at reflux temperature for 2-5 days, applied to the preparative-TLC and eluted with  $CHCl_3$ -MeOH-2N  $NH_3$  in MeOH (10:1:1) to give the title compounds. The hydrochlorides were prepared by dissolving the title compounds in minimum EtOAc, and excess 1N HCl in ether was added until no more precipitate was apparent. The solids were filtered, washed with ether, and dried under high vacuum.



1,2,3,6-Tetrahydro-1-(N-(3-(3-imidazol-1-yl)propyl)amino)propylcarboxamido-5-methoxycarbonyl-2-oxo-6-(3,4-difluorophenyl)-4-methylpyrimidine dihydrochloride (12 mg): Anal. Calc. for  $C_{23}H_{28}F_2N_6O_4 + 2.0 \text{ HCl} + 0.6 \text{ ether} + 0.3 \text{ CH}_2\text{Cl}_2$ : C, 49.31; H, 5.76; N, 13.12. Found: C, 49.07; H, 5.78; N, 13.28.

1,2,3,6-Tetrahydro-1-(N-(3-(2-indol-3-yl)ethyl)amino)propylcarboxamido-5-methoxycarbonyl-2-oxo-6-(3,4-difluorophenyl)-4-methylpyrimidine hydrochloride (23 mg); Anal. Calc. for  $C_{27}H_{29}F_2N_5O_4 + 1.0 \text{ HCl} + 3.7 \text{ THF}$ : C, 60.58; H, 7.25; N, 8.45. Found: C, 60.84; H, 7.21; N, 8.48.

#### Example 49

6-(3,4-Difluorophenyl)-1,6-dihydro-1-methoxycarbonyl-5-(3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)-propylaminocarbonyl)-2,4-dimethylpyrimidine

a) Benzyl 3-oxo-2-(3,4-difluorobenzylidenyl)butanoate.

A mixture of 3,4-difluorobenzaldehyde (7.1 g, 50 mmol.), benzyl acetoacetate (12.48 g, 65 mmol.), acetic acid (0.15 g, 2.5 mmol.), piperidine (0.212 g, 2.5 mmol.) and benzene (300 mL) was refluxed under a dean-stark trap overnight. After the removal of solvent, the residue was then dissolved in ethyl acetate and washed with saturated  $\text{KHSO}_4$ , saturated  $\text{NaHCO}_3$ , water and then dried over  $\text{Na}_2\text{SO}_4$ . The solvent was evaporated, and the residue was flash chromatographed over silica gel (eluent: 1:1 v/v ethyl acetate-hexane) to give the product in 87% yield (13.7 g) as a yellow solid.

b) 5-Benzylloxycarbonyl-6-(3,4-difluorophenyl)-1,6-dihydro-2,4-dimethylpyrimidine.

To a stirred solution of acetamidine hydrochloride (1.42 g, 15 mmol.) in DMF (10 mL) were added a solution of potassium tert-butoxide (1.23 g, 11 mmol.) in DMF (10mL) and a solution of the above yellow solid (3.16

g, 10 mmol.) in DMF (10 mL) at 0°C. After the mixture was stirred for 15 min at 0°C, p-toluenesulfonic acid monohydrate (3.8 g, 20 mmol.) was added. The mixture was heated at 100-110°C for 2 hrs. After cooling, it was quenched with 2N aqueous NaOH solution and extracted with ether. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated. The residue was flash chromatographed over silica gel (eluent: 100:5 v/v ethyl acetate-2M ammonia in methanol) to give the product in 42% yield (1.5 g) as an off-white solid.

**c) 5-Benzylloxycarbonyl-6-(3,4-difluorophenyl)-1,6-dihydro-1-methoxycarbonyl-2,4-dimethylpyrimidine.**

To a stirred slurry of NaH (59 mg, 60% in mineral oil, 1.47mmol.) in THF (5 mL) was added a solution of the above off-white solid (0.5 g, 1.4 mmol.) in THF (10 mL) at 0°C. After 5 min, methyl chloroformate (0.16 g, 1.7 mmol.) was added at 0°C. Stirring was continued at room temperature for 30 min. The mixture was quenched with brine and extracted with ethyl acetate. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to give a quantitative yield of the product as a yellow solid.

**d) 5-Carboxy-6-(3,4-difluorophenyl)-1,6-dihydro-1-methoxycarbonyl-2,4-dimethylpyrimidine.**

A solution of the above yellow solid (0.63 g, 1.52 mmol) in methanol (20 mL) was subjected to hydrogenation with a H<sub>2</sub> balloon in the presence of palladium (63 mg, 5% on C). The reaction was carried out at room temperature for 30 min. The catalyst was then filtered off and the solvent was removed in vacuo to give the product in 99% yield (0.487 g) as an off-white solid.

**e) 6-(3,4-Difluorophenyl)-1,6-dihydro-1-methoxycarbonyl-5-(3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)-propylaminocarbonyl)-2,4-**

**dimethylpyrimidine.**

A mixture of the above off-white solid (0.070 g, 0.22 mmol.), 4-dimethylaminopyridine (0.040 g, 0.33 mmol.), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.060 g, 0.30 mmol.) and CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was stirred at room temperature for 0.5 hr. After the addition of 3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propylamine (0.075 g, 0.27 mmol.), the mixture was refluxed overnight. To the mixture was added another 25 mL of CH<sub>2</sub>Cl<sub>2</sub> and washed with saturated NH<sub>4</sub>Cl solution. After the removal of the solvent, the residue was flash chromatographed over silica gel (eluent: 85:15 v/v ethyl acetate-methonal) to give the title compound in 42% yield (0.052 g) as a white solid: mp 55-57°C. Anal. Calcd. for C<sub>31</sub>H<sub>36</sub>F<sub>2</sub>N<sub>4</sub>O<sub>5</sub>·0.5CH<sub>2</sub>Cl<sub>2</sub>: C, 60.52; H, 5.97; N, 8.96. Found: C, 60.61; H, 6.09; N, 8.94.

**Example 50**

**6-(3,4-Difluorophenyl)-1,6-dihydro-5-(3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propylaminocarbonyl)-1-methoxymethyl-2,4-dimethylpyrimidine**

**a) 5-Benzyloxycarbonyl-6-(3,4-difluorophenyl)-1,6-dihydro-1-methoxymethyl-2,4-dimethylpyrimidine.**

To a stirred slurry of NaH (24 mg, 60% in mineral oil, 0.6 mmol.) in THF (5 mL) was added a solution of 5-benzyloxycarbonyl-6-(3,4-difluorophenyl)-1,6-dihydro-2,4-dimethylpyrimidine (0.2 g, 0.56 mmol.) in THF (10 mL) at 0°C. After 10 min, chloromethyl methyl ether (0.043 mL, 0.57 mmol.) was added at 0°C. Stirring was continued at room temperature for 3 hrs. The mixture was quenched with brine and extracted with ethyl acetate. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to give the product in 44.5% yield as a yellow oil.

**b) 5-Carboxy-6-(3,4-difluorophenyl)-1,6-dihydro-1-**

**methoxymethyl-2,4-dimethylpyrimidine.**

A solution of the above yellow oil (0.17 g, 0.43 mmol) in methanol (20 mL) was subjected to hydrogenation with a H<sub>2</sub> balloon in the presence of palladium (34 mg, 5% on C). The reaction was carried out at room temperature for 0.5 hr. The catalyst was then filtered off and the solvent was removed in vacuo to give the product in 100% yield (0.13 g) as an off-white solid.

**c) 6-(3,4-Difluorophenyl)-1,6-dihydro-5-(3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propylaminocarbonyl)-1-methoxymethyl-2,4-dimethylpyrimidine.**

A mixture of 5-carboxy-6-(3,4-difluoro-phenyl)-1,6-dihydro-1-methoxymethyl-2,4-dimethylpyrimidine (0.13 g, 0.42 mmol.), 4-dimethylaminopyridine (0.1 g, 0.84 mmol.), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.16 g, 0.82 mmol.) and CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was stirred at room temperature for 0.5 hr. After the addition of 3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)propylamine (0.17 g, 0.62 mmol.), the mixture was refluxed overnight. To the mixture was added another 25 mL of CH<sub>2</sub>Cl<sub>2</sub> and washed with saturated NH<sub>4</sub>Cl solution. After removal of the solvent, the residue was flash chromatographed over silica gel (eluent: 80:20 v/v ethyl acetate- methanol) to give the title compound in 32% yield (0.075 g) as a pale yellow solid: mp 53-57°C. Anal. Calcd. for C<sub>31</sub>H<sub>38</sub>F<sub>2</sub>N<sub>4</sub>O<sub>4</sub>·0.25CHCl<sub>3</sub>: C, 62.71; H, 6.44; N, 9.36. Found: C, 62.62; H, 6.79; N, 9.19.

**Example 51**

**1,6-Dihydro-5-methoxycarbonyl-1-(5-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)pentyl)-4-methyl-6-(4-nitrophenyl)-pyrimidine**

**a) 1,6-Dihydro-5-methoxycarbonyl-4-methyl-6-(4-nitrophenyl)-pyrimidine.**

Sodium (0.55 g, 23.9 mmol) was allowed to react with

anhydrous EtOH (100 mL). Then the solution was cooled by an ice water bath when formamidine acetate (2.29 g, 22.0 mmol) and methyl 2-(4-nitrobenzylidenyl)acetoacetate (5.00 g, 20.1 mmol) were added. The mixture was stirred at room temperature for 3 h. The product was filtered off as a yellow powder (4.68 g, 80%). It was mixed with p-toluenesulfonic acid monohydrate (6.7 g, 35.2 mmol) in dry DMSO (125 mL) and heated at 110°C for 3 h. Ice water (450 mL) was added and the product as a tosylate was filtered off as an off-white solid (5.55 g, 78%).

**b) 1-(5-Chloropentyl)-1,6-dihydro-5-methoxycarbonyl-4-methyl-6-(4-nitrophenyl)pyrimidine.**

The above solid (2.44 g, 5.45 mmol) was added to dry THF (50 mL) containing sodium hydride (60% oil dispersion, 480 mg, 12.0 mmol) and cooled by an ice water bath. Then 1-bromo-5-chloropentane (3 mL, 22.8 mmol) was added. The mixture was stirred at room temperature for 7 h before ice water was added. Extraction with EtOAc gave a dark oil (4.455 g) which was flash chromatographed over silica gel (120 g) eluting with EtOAc/hexane/Et<sub>3</sub>N (15:15:1) to afford a brown oil (1.43 g, 69%).

**c) 1,6-Dihydro-5-methoxycarbonyl-1-(5-(4-methoxycarbonyl-4-phenyl-piperidin-1-yl)pentyl)-4-methyl-6-(4-nitrophenyl)-pyrimidine.**

The above oil (220 mg, 0.58 mmol) was mixed with 4-methoxy-carbonyl-4-phenylpiperidine (127 mg, 0.58 mmol) and potassium iodide (106 mg, 0.64 mmol) in dry glyme (4 mL) cooled by an ice water bath. Then sodium hydride (24 mg, 60% oil dispersion, 0.60 mmol) was added. The mixture was heated at reflux overnight and more KI (106 mg) was added. Reflux was continued for two more days. Ice water was added. Extraction with EtOAc (3 x 3 mL) gave a brown oil (158 mg). It was

dissolved in  $\text{CHCl}_3/\text{EtOAc}$  and flash chromatographed over silica gel (16 g) eluting with  $\text{EtOAc}/\text{MeOH}/\text{Et}_3\text{N}$  (20:1:1) to afford a yellow oil (89 mg, 27%). Anal. Calcd. for  $\text{C}_{31}\text{H}_{38}\text{N}_4\text{O}_6 \cdot 3/4\text{H}_2\text{O}$ : C, 64.62; H, 6.91; N, 9.72. Found: C, 64.56; H, 6.84; N, 9.76.

**Example 52**

**6-(2,4-Difluorophenyl)-1,6-dihydro-1-(5-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)-pentyl)-2,4-dimethyl-5-methylaminocarbonyl-pyrimidine**

**a) Benzyl 3-oxo-2-(2,4-difluorobenzylidenyl)butanoate.**  
A mixture of 2,4-difluorobenzaldehyde (7.1 g, 50 mmol.), benzyl acetoacetate (12.48 g, 65 mmol.), acetic acid (0.15 g, 2.5 mmol.), piperidine (0.212 g, 2.5 mmol.) and 2-propanol (300 mL) was stirred at room temperature for two days. After the removal of solvent, the residue was then dissolved in ethyl acetate and washed with saturated  $\text{KHSO}_4$ , saturated  $\text{NaHCO}_3$ , water and then dried over  $\text{Na}_2\text{SO}_4$ . The solvent was evaporated, and the residue was flash chromatographed over silica gel (eluent: 1:5 v/v ethyl acetate-hexane) to give the product in 91% yield (14.3 g) as a yellow solid.

**b) 5-Benzylloxycarbonyl-6-(2,4-difluorophenyl)-1,6-dihydro-2,4-dimethylpyrimidine.** To a stirred solution of acetamidine hydrochloride (2.84 g, 30 mmol.) in DMF (20 mL) were added a solution of potassium tert-butoxide (2.46 g, 22 mmol.) in DMF (20mL) and a solution of the above yellow solid (6.32 g, 20 mmol.) in DMF (20 mL) at  $0^\circ\text{C}$ . After the mixture was stirred for 15 min at  $0^\circ\text{C}$ , *p*-toluenesulfonic acid monohydrate (7.6 g, 40 mmol.) was added. The mixture was heated at  $100\text{--}110^\circ\text{C}$  for 2 hrs. After cooling, it was quenched with 2N aqueous NaOH solution and extracted with ether. The organic layer was dried over  $\text{Na}_2\text{SO}_4$  and evaporated. the residue was flash chromatographed over silica gel (eluent: 100:5 v/v ethyl acetate-2M ammonia in

Methanol) to give the product in 42% yield (1.5 g) as an off-white solid.

5        **c)     5-Benzyloxycarbonyl-1-(5-bromopentyl)-6-(2,4-difluorophenyl)-1,6-dihydro-2,4-dimethylpyrimidine.** To  
a suspension of NaH (123 mg, 60% dispersion in mineral  
oil, 3.08 mmol.) in THF (5 mL) was added a solution of  
the above off-white solid (1.0 g, 2.8 mmol.) and HMPA  
10        (0.5 g, 2.8 mmol.) in THF (5 mL) at 0°C. After 15 min,  
1,5-dibromopentane (1.53 mL, 11.2 mmol.) was added.  
The mixture was then refluxed for 30 min. The solid was  
filtered off. After the removal of the solvent, the  
residue was flash chromatographed over silica gel  
(eluent: ethyl acetate) to give the product in 78%  
15        yield (1.1 g) as a yellow oil.

20        **d)     5-Benzyloxycarbonyl-6-(2,4-difluorophenyl)-1,6-dihydro-1-(5-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)pentyl)-2,4-dimethyl-pyrimidine.** A mixture of the  
above yellow oil (1.62 g, 3.2 mmol.), 4-  
methoxycarbonyl-4-phenyl piperidine (1.4 g, 6.4 mmol.),  
potassium carbonate (1.76 g, 12.7 mmol.), sodium iodide  
(0.45 g, 3.0 mmol.) and 1,4-dioxane (15 mL) was  
25        refluxed overnight. The undissolved solid was then  
filtered off and the solvent was evaporated. The  
residue was flash chromatographed over silica gel  
(eluent: 80:20 v/v ethyl acetate-2M ammonia in  
methanol) to give the product in 66% yield (1.36 g) as  
a yellow oil.

30        **e)     5-Carboxy-6-(2,4-difluorophenyl)-1,6-dihydro-1-(5-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)pentyl)-2,4-dimethyl-pyrimidine.** A solution of the above yellow  
oil (0.36 g, 0.56 mmol) in methanol (20 mL) was  
35        subjected to hydrogenation with a H<sub>2</sub> balloon in the  
presence of palladium (36 mg, 5% on C). The reaction  
was carried out at room temperature for 30 min. The

catalyst was then filtered off and the solvent was removed *in vacuo* to give the product in quantitative yield (0.31 g) as an off-white solid.

5        f)        6-(2,4-Difluorophenyl)-1,6-dihydro-1-(5-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)-pentyl)-2,4-dimethyl-5-methylaminocarbonyl-pyrimidine. A mixture of the above off-white solid (0.244 g, 0.44 mmol.), 4-dimethylaminopyridine (0.26 g, 2.12 mmol.), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.13 g, 0.66 mmol.) and  $\text{CH}_2\text{Cl}_2$  (10 mL) was stirred at room temperature for 2 hrs. After the addition of methyl amine hydrogen chloride (0.089 g, 1.32 mmol.), the mixture was stirred at room temperature overnight. 15 To the mixture was added another 25 mL of  $\text{CH}_2\text{Cl}_2$  and washed with saturated  $\text{NH}_4\text{Cl}$  solution. After removal of the solvent, the residue was flash chromatographed over silica gel (eluent: 100:20 v/v ethyl acetate-2M ammonia in methanol) to give the title compound in 22% yield (0.055 g) as a yellow oil. Treatment of the free base with 2 equivalents of 1M HCl in ether gave the HCl salt as a pale yellow solid: mp 152-155°C. Anal. Calcd. for  $\text{C}_{32}\text{H}_{40}\text{F}_2\text{N}_4\text{O}_3 \cdot 2\text{HCl} \cdot 1.6\text{H}_2\text{O} \cdot 0.8\text{CHCl}_3$ : C, 51.57; H, 6.07; N, 7.33. Found: C, 51.38; H, 5.91; N, 7.27.

25

#### Example 53

6(R,S)-(3,4-Difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-1-(5-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)-4(S)-methyl)pentyl-2,4-dimethylpyrimidine

30

a) (S)-(+)-3-Methylpiperidine. A mixture of (+)-mandelic acid (45.64 g, 0.3 mol) in ethyl acetate (300 mL) was heated to solution and treated with 3-methylpiperidine (29.75 g, 0.3 mol). The mixture was allowed to come to room temperature before filtration. 35 The crystalline material was washed with 1:1 ethyl acetate-ether (400 mL). Two recrystallizations of this



salt from ethyl acetate gave the optically pure salt in 56% yield (21.7 g).

5        **b) (S) - (+) - N-Benzoyl-3-methylpiperidine.** The above salt  
      (21 g, 0.088 mol) was dissolved in sodium hydroxide  
      solution (1.0 N, 200 mL). The solution was cooled to  
      3°C, and benzoyl chloride (12.5 g, 0.089 mol) was added  
      dropwise over 10 min. After the addition was complete,  
10        the mixture was transferred to a separatory funnel and  
      extracted with ether. The combined extracts were dried  
      ( $\text{Na}_2\text{SO}_4$ ) and concentrated to give the pure amide in 98%  
      yield ( 17.2 g):  $[\alpha]_D +45.9$  (c 1.00,  $\text{CH}_3\text{OH}$ ).

15        **c) (S) - (-) - 2-Methyl-1,5-dibromopentane.** To the above  
      amide powder was added phosphorus tribromide (7.81 mL,  
      d 2.85, 0.082 mol) at 5°C over 20 min with vigorous  
      stirring. After the addition, the mixture was warmed to  
      room temperature, and  $\text{Br}_2$  (4 mL, 0.082 mol) was added  
      dropwise over 10 min. The mixture was then allowed to  
20        stand at room temperature overnight and distilled under  
      vacuum (0.5-1 mm Hg) until the head temperature reached  
      80°C. The distillate was dissolved in hexane (100 mL)  
      and washed successively with water (20 mL),  
      concentrated sulfuric acid (4x30 mL), water (20 mL),  
25        NaOH solution (1N, 2x40 mL), and water (20 mL). The  
      hexane solution was then dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated  
      to give the product in 31% yield (6.4 g) as a light  
      yellow liquid.

30        **d) 1 - (5-Bromo-4 (S) -methylpentyl) - 6 (R, S) - (3,4 -**  
      **difluorophenyl) - 1,6-dihydro-5-methoxycarbonyl-2,4 -**  
      **dimethylpyrimidine.** To a suspension of NaH (47mg, 60%  
      dispersion in mineral oil, 1.17 mmol.) in THF (3 mL)  
      was added a solution of 6-(3,4-difluoro-phenyl)-1,6-  
35        dihydro-5-methoxycarbonyl-2,4-dimethylpyrimidine (0.3  
      g, 1.07 mmol.) and HMPA (0.193 g, 1.07 mmol.) in THF (4  
      mL) at 0°C. After 10 min, a solution of (-)-2-methyl-

1,5-dibromopentane (0.86 g, 3.53 mmol.) in THF (5 mL) was added. The mixture was then refluxed for 10 min. The solid formed was filtered off. After the removal of the solvent, the residue was flash chromatographed over silica gel (eluent: 100:5 v/v ethyl acetate-2.0M ammonia in methanol) to give the product in 36% yield (0.169 g) as a yellow oil.

e) 6(R,S)-(3,4-Difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-1-(5-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)-4(S)-methyl)pentyl-2,4-dimethylpyrimidine. A mixture of the above yellow oil (0.169 g, 0.38 mmol.), 4-methoxycarbonyl-4-phenylpiperidine (0.167 g, 0.76 mmol.), potassium carbonate (0.21 g, 1.52 mmol.), sodium iodide (0.057 g, 0.38 mmol.) and 1,4-dioxane (8 mL) was refluxed overnight. The undissolved solid was then filtered off and the solvent was evaporated. The residue was flash chromatographed over silica gel (eluent: 100:5 v/v ethyl acetate-2M ammonia in methanol) to give the title compound in 11% yield (0.025 g) as a yellow oil. Treatment of the free base with 2 equivalents of 1M HCl in ether gave the HCl salt as a light yellow solid: mp 155-158°C. Anal. Calcd. for  $C_{33}H_{41}F_2N_3O_4 \cdot 2HCl \cdot 0.5H_2O$ : C, 59.72; H, 6.64; N, 6.33. Found: C, 59.47; H, 6.66; N, 6.10.

#### Example 54

6-(3,4-Difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-1-(3-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)methyl)benzyl-2,4-dimethylpyrimidine

a) 1-(3-Bromomethylbenzyl)-6-(3,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2,4-dimethylpyrimidine. To a suspension of NaH (31 mg, 60% dispersion in mineral oil, 0.77 mmol.) in THF (5 mL) was added a solution of 6-(3,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2,4-dimethylpyrimidine (0.3 g, 1.07 mmol.) and HMPA

(0.193 g, 1.07 mmol.) in THF (5 mL) at 0°C. After 15 min,  $\alpha,\alpha'$ -dibromo-m-xylene (0.99 g, 3.75 mmol.) was added. The mixture was then refluxed for 15 min. The solid was filtered off. After the removal of the solvent, the residue was flash chromatographed over silica gel (eluent: ethyl acetate) to give the product in 91% yield (0.45 g) as a yellow oil.

**b) 6-(3,4-Difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-1-(3-(4-methoxycarbonyl-4-phenyl-4-phenylpiperidin-1-yl)methyl)benzyl-2,4-dimethylpyrimidine.**

A mixture of the above yellow oil (0.45 g, 0.97 mmol.), 4-methoxycarbonyl-4-phenyl piperidine (0.42 g, 1.9 mmol.), potassium carbonate (0.67 g, 4.86 mmol.), sodium iodide (0.14 g, 0.97 mmol.) and 1,4-dioxane (10 mL) was refluxed overnight. The undissolved solid was then filtered off and the solvent was evaporated. The residue was flash chromatographed over silica gel (eluent: 100:5 v/v ethyl acetate-2M ammonia in methanol) to give the title compound in 17% yield (0.10 g) as a yellow oil. Treatment of the free base with 2 equivalents of 1M HCl in ether gave the HCl salt as an off-white solid: mp 181-183°C. Anal. Calcd. for  $C_{35}H_{37}F_2N_3O_4 \cdot 2HCl \cdot 1.0H_2O$ : C, 60.69; H, 5.97; N, 6.07. Found: C, 60.73; H, 5.77; N, 5.94.

#### Example 55

**6-(3,4-Difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2,4-dimethyl-1-(5-(3-phenylpropylamino)pentyl)-pyrimidine**

A mixture of 1-(5-bromopentyl)-6-(3,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2,4-dimethylpyrimidine (0.186 g, 0.433 mmol.), 3-phenyl-1-propylamine (0.12 g, 0.89 mmol.), potassium carbonate (0.3 g, 2.17 mmol.), sodium iodide (70 mg, 0.46 mmol.) and 1,4-dioxane (8 mL) was refluxed overnight. The undissolved solid was

then filtered off and the solvent was evaporated. The residue was flash chromatographed over silica gel (eluent: 100:20:10 v/v/v CHCl<sub>3</sub>-methanol-2M ammonia in methanol) to give the product in 54% yield (0.114 g) as a yellow oil. Treatment of the free base with 2 equivalents of 1M HCl in ether gave the HCl salt as a white solid: mp 95-97°C. Anal. Calcd. for C<sub>28</sub>H<sub>35</sub>F<sub>2</sub>N<sub>3</sub>O<sub>2</sub>·2HCl·0.5CH<sub>2</sub>Cl<sub>2</sub>: C, 57.15; H, 6.39; N, 7.02. Found: C, 57.09; H, 6.65; N, 6.85.

#### Example 56

**(+)-6-(3,4-Difluorophenyl)-1,6-dihydro-1-(4-hydroxy-5-(4-(2-pyridyl)piperidin-1-yl)pentyl)-5-methoxycarbonyl-2,4-dimethylpyrimidine**

##### a) 3-Bromopropylepoxiide.

To a solution of 5-bromo-1-pentene (2.15 g, 14.4 mmol.) in CH<sub>2</sub>Cl<sub>2</sub> (40 mL) was added MCPBA (3.0 g, 17.3 mmol.) at 0°C slowly. After stirred at room temperature overnight, the mixture was poured into a mixture of ice and 2N NaOH solution. The separated aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layer was then washed with water, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. The concentrated mixture was flash chromatographed over silica gel (eluent: CH<sub>2</sub>Cl<sub>2</sub>) to give the product in 92% yield (2.19 g) as a pale yellow liquid.

##### b) 1-(4,5-Epoxyypentyl)-6-(3,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2,4-dimethylpyrimidine.

To a suspension of NaH (78 mg, 60% dispersion in mineral oil) in THF (10 mL) was added a solution of 6-(3,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2,4-dimethylpyrimidine (0.5 g, 1.78 mmol.) and HMPA (0.3 mL, 1.78 mmol.) in THF (5 mL) at 0°C. After 20 min, the above pale yellow liquid (0.6 g, 3.6 mmol.) was added. The mixture was then refluxed 2hrs. After the removal of the solvent, the residue was flash chromatographed over silica gel (eluent:100:5 v/v ethyl acetate-2.0M

ammonia in methanol) to give the product in 62% yield (0.4 g) as a yellow oil.

- 5 c) 6-(3,4-Difluorophenyl)-1,6-dihydro-1-(4-hydroxy-5-(4-(2-pyridyl)piperidin-1-yl)pentyl)-5-methoxycarbonyl-2,4-dimethylpyrimidine.

A mixture of the above yellow oil (0.48 g, 1.32 mmol.), 4-(2-pyridyl)piperidine (0.32 g, 1.98 mmol.) and 1,4-dioxane (10 mL) was refluxed overnight. The  
10 concentrated mixture was then flash chromatographed over silica gel (eluent: 80:20 v/v ethyl acetate-2.0M ammonia in methanol) to give all four diastereomers in 43% yield (0.3 g). Chiral HPLC separation gave the title enantiomer which was converted to a HCl salt:  $[\alpha]_D$   
15 = 120.6 (c 0.7, MeOH); mp 163-165°C. Anal. Calcd. for  $C_{29}H_{36}F_2N_4O_3 \cdot 3HCl \cdot 0.7CHCl_3$ : C, 49.57; H, 5.56; N, 7.79. Found: C, 49.41; H, 5.96; N, 7.38.

#### Example 57

- 20 6-(3,4-Difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2,4-dimethyl-1-(5-(4-(2-pyridyl)piperidin-1-yl)-4-oxo)pentyl pyrimidine

To a solution of oxalyl chloride (8 mg, 0.06 mmol.) in  $CH_2Cl_2$  (0.25 mL) was added a solution of DMSO (10 mg, 0.14 mmol.) in  $CH_2Cl_2$  (0.3 mL) at -78°C. After 3 min, a  
25 solution of 6-(3,4-difluorophenyl)-1,6-dihydro-1-(4-hydroxy-5-(4-(2-pyridyl)-piperidin-1-yl)pentyl)-5-methoxycarbonyl-2,4-dimethylpyrimidine (30 mg, 0.057 mmol.) in  $CH_2Cl_2$  (1 mL) was added to the mixture which  
30 was stirred for another 15 min. The mixture was treated with triethylamine (0.04 mL) and stirred for another 5 min. Then it was allowed to warm up to room temperature. After the addition of water, it was washed with 1N NaOH and water. The organic layer was dried  
35 over  $Na_2SO_4$  and concentrated. The residue was purified by preparative TLC (eluent: 100:20 v/v ethyl acetate-2.0M ammonia in methanol) to give the title compound in

43% yield (13 mg) as a yellow oil. Treatment of the free base with 3 equivalents of 1M HCl in ether gave the HCl salt as a pale yellow solid: mp 135-137°C. Anal. Calcd. for  $C_{29}H_{34}F_2N_4O_3 \cdot 3HCl \cdot 2H_2O \cdot 0.9CH_2Cl_2$ : C, 48.11; H, 5.78; N, 7.51. Found: C, 47.99; H, 6.08; N, 7.35.

**Example 58**

(+) - 4 - (3,4,5-Trifluorophenyl) - 3,4-dihydro-5-methoxycarbonyl-6-methyl-3-(5-(4-(2-pyridyl)piperidin-1-yl)-pentyl-2(1H)-pyrimidone

a) 3-(5-Bromopentyl)-4-(3,4,5-trifluorophenyl)-3,4-dihydro-5-methoxycarbonyl-6-methyl-2(1H)-pyrimidone.

To a suspension of NaH (0.23 g, 60% dispersion in mineral oil, 5.8 mmol.) in THF (40 mL) was added a solution of 6-(3,4,5-trifluorophenyl-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-pyrimidine (0.6 g, 1.9 mmol.) and HMPA (0.33 mL, 1.9 mmol.) in THF (10 mL) at 0°C. After 20 min, 1,5-dibromopentane (1.75 g, 9.4 mmol.) was added. The mixture was then refluxed for 2 hrs and quenched by water. The mixture was partitioned between ethyl acetate and water. The organic layer was separated, treated with 6N HCl (10 mL) solution and stirred at room temperature for 1 hr. It was then separated and dried over  $Na_2SO_4$ . After the removal of solvent, the residue was flash chromatographed over silica gel (eluent: 80:20 v/v hexane-ethyl acetate) to give the product in 73% yield (0.62 g) as a yellow oil.

b) (+) - 4 - (3,4,5-Trifluorophenyl) - 3,4-dihydro-5-methoxycarbonyl-6-methyl-3-(5-(4-(2-pyridyl)piperidin-1-yl)-pentyl-2(1H)-pyrimidone. A mixture of 3-(5-bromopentyl)-4-(3,4,5-trifluorophenyl)-3,4-dihydro-5-methoxycarbonyl-6-methyl-2(1H)-pyrimidone (0.3 g, 0.7 mmol.), 4-(2-pyridyl) piperidine (0.22 g, 1.4 mmol.), potassium carbonate (0.5 g, 3.6 mmol.), sodium iodide (0.1g, 0.7 mmol.) and acetone (20 mL) was refluxed overnight. The undissolved solid was then filtered off

and the solvent was evaporated. The residue was flash chromatographed over silica gel (eluent: 80:20 v/v ethyl acetate-2.0M ammonia in Methanol) to give the racemic product in 85% yield (0.3 g) as a yellow oil. Chiral HPLC separation afforded the title enantiomer which was converted to a HCl salt:  $[\alpha]_D = 122$  (c 4.1, MeOH); mp 125-127°C. Anal. Calcd. for  $C_{28}H_{33}F_3N_4O_3 \cdot 2HCl \cdot 2H_2O \cdot 0.2Et_2O$ : C, 52.86; H, 6.32; N, 8.56. Found: C, 52.66; H, 6.37; N, 8.15.

**E x a m p l e 5 9**  
**4-(3,4,5-Trifluorophenyl)-3,4-dihydro-5-methoxycarbonyl-6-methyl-3-(3-(4-(2-pyridyl)piperidin-1-yl)propyloxycarbonyl)-2(1H)-pyrimidone.**

**a) 1-(3-Hydroxypropyl)-4-(2-pyridyl)piperidine.**

A mixture of 4-(2-pyridyl)piperidine (200 mg, 1.23 mmol), 3-bromopropanol (135 mL, 1.49 mmol), potassium carbonate (620 mg, 4.49 mmol) and a catalytic amount of sodium iodide in acetone (10 mL) was heated at reflux overnight. Filtration followed by evaporation of the solvent gave a light brown oil (324 mg) which was dissolved in  $CHCl_3$  and flash chromatographed over silica gel (20 g) eluting with EtOAc/MeOH/ $Et_3N$  (20:1:1) to afford a light brown solid (166 mg, 61%).

**b )**  
**4-(3,4,5-Trifluorophenyl)-3,4-dihydro-5-methoxycarbonyl-6-methyl-3-(3-(4-(2-pyridyl)piperidin-1-yl)propyloxycarbonyl)-2(1H)-pyrimidone.**

A mixture of 1-(3-hydroxypropyl)-4-(2-pyridyl)-piperidine (72 mg, 0.33 mmol) and 4-(3,4,5-trifluorophenyl)-3,4-dihydro-5-methoxycarbonyl-6-methyl-3-(4-nitrophenoxy carbonyl)-2(1H)-pyrimidine (152 mg, 0.33 mmol) in dry THF (8 mL) was heated at reflux overnight. The residue obtained after evaporation of the solvent was dissolved in EtOAc and flash chromatographed over silica gel (18 g) eluting with

EtOAc/MeOH/Et<sub>3</sub>N (100:3:3) to afford an off-white solid (133 mg, 75%). It was dissolved in CH<sub>2</sub>Cl<sub>2</sub> and treated with 1M HCl in ether (0.6 mL) to give an off-white solid: mp 154°C (dec.). Anal. Calcd. for C<sub>27</sub>H<sub>29</sub>F<sub>3</sub>N<sub>4</sub>O<sub>5</sub>·2HCl·2H<sub>2</sub>O: C, 49.47; H, 5.38; N, 8.55. Found: C, 49.48; H, 5.16; N, 8.35.

**Example 60**

(+)-1,2,3,6-Tetrahydro-1-{N-[4-cyano-4-(phenyl)cyclohex-1-yl]ethyl}carboxamido-5-methoxy carbonyl-4-methoxymethyl-6-(3,4-difluorophenyl)-2-oxopyrimidine hydrochloride.

**a) 2-[4-Cyano-4-(phenyl)cyclohex-1-yl]ethylamine.**

A mixture of 4-phenyl-4-cyanocyclohexanone (5.00 g, 25.09 mmol) and ethylenediamine (5.58) and p-toluene sulfonic acid in benzene (200 mL) were refluxed for 4 h in a Dean-Stork set-up to remove the water formed. Solvent was evaporated and the residue was redissolved in methanol and cooled to 0 °C. To this, sodium borohydride (1.5 g) was added in portions and the mixture was stirred at room temperature for 3 h. Solvent was evaporated, the residue was dissolved in dichloromethane (300 mL), washed with brine (2 X 200 mL) and dried (sodium sulfate). Solvent was evaporated and the residue was dried under vacuum to leave the product as an oil ( 5.2 g). The <sup>1</sup>H-NMR showed this product to be pure and found to contain the cis/trans isomers in the ratio of about 9:1. It was used as was in the next step.

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**b) (+)-1,2,3,6-Tetrahydro-1-{N-[4-cyano-4-(phenyl)cyclohex-1-yl]ethyl}carboxamido-5-methoxycarbonyl-4-methoxymethyl-6-(3,4-difluorophenyl)-2-oxopyrimidine hydrochloride.**

A solution of (+)-6-(3,4-difluorophenyl)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methoxymethyl-1-(4-nitrophenoxy)carbonylpyrimidine (0.220 g, 0.448



mmol), 2-[4-cyano-4-(phenyl)cyclohex-1-yl]ethylamine  
(0.130 g, 0.538 mmol) in tetrahydrofuran (100 mL) was  
stirred at room temperature for 24 hours. The reaction  
mixture was stirred for another 1 hour after addition  
of 2 mL of 6N HCl. Solvent was evaporated at reduced  
pressure and the residue was basified by treatment with  
10% aqueous KOH solution, extracted with  
dichloromethane (3 x 10 mL). The combined extracts  
were dried over potassium carbonate, and solvent  
evaporated. The crude product was purified by  
preparative thinlayer chromatography  
(dichloromethane:MeOH:2M ammonia in MeOH, 90:8:4). The  
two possible isomer were obtained in the order of less  
polar compound as the minor product and the more polar  
compound as the major component (yields: 16 mg minor  
and 160 mg major isomer). The HCl salts were obtained  
by treatment with 1N HCl in ether. The minor isomer HCl  
salt:m.p. 124-126 °C;  $[\alpha]_D = +112$  (c = 0.21 g in 100 mL  
CHCl<sub>3</sub>); Anal. Calcd. for C<sub>30</sub>H<sub>34</sub>N<sub>5</sub>O<sub>5</sub>F<sub>2</sub>Cl.0.5 chloroform.  
0.5 ether: C, 54.61; H, 5.57; N, 9.80. Found: C,  
54.43; H, 5.29; N, 9.54. The major isomer HCl salt: m.  
p. 136-138 °C;  $[\alpha]_D = +142$  (c = 0.21 g in 100 mL CHCl<sub>3</sub>);  
Anal. Calcd. for C<sub>30</sub>H<sub>34</sub>N<sub>5</sub>O<sub>5</sub>F<sub>2</sub>Cl.0.4 chloroform: C, 54.84;  
H, 5.21; N, 10.52. Found: C, 55.16; H, 5.39; N, 10.42.

25

**General Procedure for the Preparation of 4,4-Diarylpiperidines:**

A mixture of 0.5 g of 4-aryl-4-hydroxy piperidine, 3 mL of the aromatic substrate, and 1 g of aluminum chloride was stirred at room temperature for 3 days. The reaction mixture was poured over 10 mL of ice, diluted with t-butyl-methyl ether, the resulting hydrochloride salt was filtered, washed with water and ether, dried, and used in the next step after spectral characterization.

**4-Phenyl-4-(4-thiomethoxy-phenyl)-piperidine hydrochloride:**

From 4-phenyl-4-hydroxy-piperidine and thioanisole (82%), Anal. Calc. for  $C_{18}H_{21}N_1S_1+HCl+0.2H_2O$ : C, 66.83; H, 6.98; N, 4.33. Found: C, 66.71; H, 6.81; N, 4.24.

**4-(4-Fluorophenyl-4-(4-thiomethoxy-phenyl)-piperidine hydrochloride:**

From 4-(4-fluoro-phenyl)-4-hydroxy-piperidine and thioanisole (59%), Anal. Calc. for  $C_{18}H_{20}F_1N_1S_1+HCl+0.35CH_2Cl_2$ : C, 60.14; H, 5.56; N, 3.90. Found: C, 59.96; H, 5.95; N, 3.81.

**4-(4-Fluorophenyl-4-(2-methoxy-5-fluoro-phenyl)-piperidine hydrochloride:**

From 4-(4-fluorophenyl)-4-hydroxy-piperidine and 4-fluoroanisole (78%), Anal. Calc. for  $C_{18}H_{19}N_1F_2O_1+HCl+0.2H_2O$ : C, 62.96; H, 5.99; N, 4.08. Found: C, 62.72; H, 6.06; N, 4.06.

**Bis-4-(4-Chlorophenyl)-piperidine hydrochloride:**

From 4-(4-chlorophenyl)-4-hydroxy-piperidine and chlorobenzene (92%), Anal. Calc. for  $C_{17}H_{17}N_1Cl_2+HCl$ : C, 59.58; H, 5.29; N, 3.90. Found: C, 59.58; H, 5.28; N, 3.90.

**4-Phenyl-4-(4-Hydroxy-phenyl)-piperidine hydrochloride:**

From 4-phenyl-4-hydroxy-piperidine and phenol (58%).

**General Procedure for the preparation of 4,4-diaryl-N-(3-amino)-propylpiperidines:**

A mixture of 4,4-diarylpiperidine hydrochloride (0.100 mmol), (3-bromopropyl)-carbamic acid tert-butyl ester (0.100 mmol), diisopropylethylamine (1 mL), and dioxane (2 mL) were heated at reflux

5 temperature for 2 days, cooled, chromatographed (silica prep-TLC plates) to give the BOC protected 4,4-diaryl-N-aminopropylpiperidine.

The BOC protected amine was dissolved in 1:1 TFA-dichloromethane, stirred for 6 hours, concentrated in  
10 vacuo, and the crude product was chromatographed (silica gel prep-TLC plates) to give 4,4-diaryl-N-(3-amino)propylpiperidines which were used after spectral characterization.

15 **General Procedure for the Preparation of Dihydropyrimidinones:**

**Method A: Reaction of piperidines with bromopropylcarbamoyl-dihydropyrimidinones:**

A mixture of the 3-{3-bromopropylcarbamoyl}-  
20 4-(3,4-difluoro-phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid methyl ester (45 mg, 0.1 mmol) and 0.1 mmol of 4,4-diarylpiperidine hydrochloride in a mixture of dioxane-diisopropylethylamine (2-0.5 mL) was heated  
25 at reflux temperature for 2 days, cooled, applied to a preparative-TLC plate and eluted with MeOH-EtOAc (2-3%) to give the dihydro-pyrimidine free base as the product. The free base was dissolved in a minimum of EtOAc and excess 1 N HCl in ether was  
30 added. The product was filtered, washed with ether, and dried.

**Example 61:**

3-{3-[(4-phenyl)-4-(4-thiomethoxy-phenyl)-piperidin-1-yl]-propyl-  
35 carbamoyl}-4-(3,4-difluoro-phenyl)-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid methyl ester

**hydrochloride.**

Prepared by method A. 63% yield. Anal. Calc. for  $C_{35}H_{38}N_4F_2O_4S_1 + HCl + 0.2CHCl_3$ : C, 59.62; H, 5.57; N, 7.90. Found: C, 60.07; H, 6.27; N, 7.40.

5 **Example 62:**

3-{3-[(4-phenyl)-4-(4-thiomethoxy-phenyl)-piperidin-1-yl]-propylcarbamoyl}-4-(3,4-difluorophenyl)-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid methyl ester hydrochloride.

Prepared by method A. 63% yield. Anal. Calc. for  $C_{35}H_{37}N_4F_3O_4S_1 + HCl$  + ether: C, 60.26; H, 6.22; N, 7.21. Found: C, 60.46; H, 6.58; N, 7.41.

**Example 63:**

15 3-{3-[4-(4-Fluorophenyl)-4-(2-methoxy-5-methyl-phenyl)piperidin-1-yl]-propylcarbamoyl}-4-(3,4-difluoro-phenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester hydrochloride.

Prepared by method A. 63% yield. Anal. Calc. for  $C_{35}H_{36}N_4F_4O_5 + HCl + H_2O$ : C, 58.13; H, 5.44; N, 7.75. Found: C, 57.97; H, 5.55; N, 7.31.

**Example 64:**

25 3-{3-[Bis-4-(4-Chlorophenyl)piperidin-1-yl]-propylcarbamoyl}-4-(3,4-difluorophenyl)-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid methyl ester hydrochloride.

30 Prepared by method A. 71% yield. Anal. Calc. for  $C_{34}H_{34}Cl_2N_4F_2O_4 + HCl$  + ether: C, 58.35; H, 5.80; N, 7.16. Found: C, 58.23; H, 5.71; N, 7.39.

**Example 65:**

35 3-{3-[(4-phenyl)-4-(4-hydroxyphenyl)piperidin-1-yl]-propyl-carbamoyl}-4-(3,4-difluorophenyl)-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid methyl ester hydrochloride.

Prepared by method A. 63% yield. Anal. Calc. for  $C_{34}H_{36}N_4F_2O_{51}+HCl+1.4\text{ethanol}$ : C, 61.08; H, 6.61; N, 7.75. Found: C, 60.86; H, 6.77; N, 7.32.

Method B. Reaction of 4,4-diaryl-N-(3-aminopropyl)piperidines with p-nitrophenylcarbamoyleldihydropyrimidinones:

Example 66:

3,6-Dihydro-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1-{N-[4,4-

10 bis-(4-fluorophenyl)-piperidine-1-yl]-propyl}carboxamido-

6-(2,3,6-trifluorophenyl)-pyrimidine dihydrochloride.

a) Methyl 2-methoxyacetyl-3-(2,3,6-trifluorophenyl)acrylate. A mixture of 2,3,6-

15 trifluorobenzaldehyde (5.2 g, 33 mmol), methyl 4-methoxyacetoacetate (5.7 ml, 39 mmol), and

piperidinium acetate (catalytic amount) in benzene (10 ml) was stirred at room temperature for 3 days.

20 The solvent was evaporated, and the residue was chromatographed on silica gel (hexane/ether = 7/1) to yield the title compound (3.4 g, 36%) as a mixture of *cis* and *trans* isomers as a colorless oil.

b) 1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methoxymethyl-6-(2,3,6-trifluorophenyl)pyrimidine.

25 A mixture of methyl 2-methoxyacetyl-3-(2,3,6-trifluorophenyl)-acrylate (3.4 g, 11.8 mmol), O-methylisourea hydrogen hemisulfate (2.3 g, 16.5 mmol), and 4-dimethylaminopyridine (32.0 g, 16.5 mmol) in ethanol (10 ml) was stirred at 65 °C for 24

30 hours, cooled and filtered. The filtrate was concentrated and chromatographed on silica gel (hexane/ether = 2/1) to yield the title compound (0.78 g, 20 % yield) as a colorless oil.

35 c) 1,6-Dihydro-2-methoxy-5-methoxycarbonyl-4-methoxymethyl-1-(4-nitrophenyloxy)carbonyl-6-(2,3,6-trifluorophenyl)-pyrimidine.

To a solution of 1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methoxymethyl-6-(2,3,6-trifluorophenyl)-pyrimidine (0.76 g, 2.2 mmol) and 4-dimethylaminopyridine (0.33 g, 2.7 mmol) in  $\text{CH}_2\text{Cl}_2$  (5 ml), at room temperature, was added 4-nitrophenyl chloroformate (0.54 g, 2.7 mmol). The reaction solution was stirred at room temperature for 24 hours. It was filtered. The filtrate was concentrated and chromatographed on silica gel (hexane/ether = 2/1) to give the title compound (0.98 g, 87 % yield) as a pale yellow solid.

**d) 3,6-Dihydro-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1-{N-[4,4-bis-(4-fluorophenyl)-piperidine-1-yl]-propyl}carboxamido-6-(2,3,6-trifluorophenyl)-pyrimidine dihydrochloride.**

A mixture of 1,6-Dihydro-2-methoxy-5-methoxycarbonyl-4-methoxymethyl-1-(4-nitrophenoxy) carbonyl-6-(2,3,6-trifluorophenyl)pyrimidine (25 mg, 0.05 mmol) and 3-[4,4-bis-(4-fluorophenyl)-piperidin-1-yl]-propylamine (20 mg, 0.06 mmol) in  $\text{CH}_2\text{Cl}_2$  ( 3 ml ) was stirred at room temperature for 12 hours. HCl solution (6 N, 2 ml) was added. The reaction mixture was stirred at room temperature for 6 hour. KOH solution (1 N) was added to neutralize the reaction mixture, and was extracted with  $\text{CH}_2\text{Cl}_2$ . The extracts were dried ( $\text{Na}_2\text{SO}_4$ ), concentrated and the product was chromatographed on prep. TLC ( $\text{CH}_2\text{Cl}_2$  :  $\text{CH}_3\text{OH}$  : 2 N  $\text{NH}_3$  in  $\text{CH}_3\text{OH}$  = 40:2:1) to obtain the title compound (18 mg, 53%) as a colorless oil. The hydrochloride of the title compound was synthesized using HCl in ether. Calculated for  $\text{C}_{35}\text{H}_{35}\text{N}_5\text{O}_4\text{F}_5$  + 2.0 HCl: C, 55.06%; H, 4.63%; N, 7.16%. Found: C, 55.34%; H, 4.91%; N, 7.38%.

**Example 67:**

**3,6-Dihydro-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1-{N-[4-(4-chloro-phenyl)-4-(5-fluoro-2-**

**methoxy-phenyl)-piperidine-1-yl]-propyl}carboxamido-6-(3,5-difluorophenyl)-pyrimidine dihydrochloride.**

**a) Methyl 2-methoxyacetyl-3-(3,5-difluoro-phenyl)-acrylate.**

5 A mixture of 3,5-difluorobenzaldehyde (10 g, 70 mmol), methyl 4-methoxyacetoacetate ( 11 ml, 80 mmol), and piperidinium acetate (catalytical amount) in benzene (100 ml) was stirred at room temperature for 3 days. The solvent was evaporated, and the residue  
10 was chromatographed on silica gel (hexane/ether = 5/1) to give the *cis* and *trans* mixture of the title compound (3.7 g, 20% yield) as a yellow oil .

**b) 1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methoxymethyl-6-(3,5-difluoro-phenyl)-pyrimidine.**

15 A mixture of methyl 2-methoxyacetyl-3-(3,5-difluoro-phenyl)-acrylate (3.74 g, 13.8 mmol), O-methylisourea hydrogen hemisulfate (2.68 g, 19.4 mmol), and 4-dimethylaminopyridine (2.37 g, 19.4 mmol) in ethanol (30 ml) was stirred at 65 °C for 2  
20 days, cooled and filtered . The filtrate was concentrated and chromatographed on silica gel (hexane/ether = 3/1) to get the title compound (1.7 g, 38 % yield) as a yellow solid.

**c) 1,6-Dihydro-2-methoxy-5-methoxycarbonyl-4-methoxymethyl-1-(4-nitrophenyloxy) carbonyl-6-(3,5-difluorophenyl)-pyrimidine.**

To a solution of 1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methoxymethyl-6-(3,5-difluorophenyl)pyrimidine (1.67 g, 5.10 mmol) and 4-dimethylaminopyridine (0.75 g, 6.1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 ml), at room temperature, was added 4-nitrophenyl chloroformate (1.24 g, 6.1 mmol). The reaction  
30 solution was stirred at room temperature for 24 hours, and filtered. The filtrate was concentrated and chromatographed on silica gel (hexane/ether =  
35 2/1) to yield the title compound (1.82 g, 72 % yield)

as a white solid.

d) 3,6-Dihydro-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1-{N-[4-(4-chloro-phenyl)-4-(5-fluoro-2-methoxy-phenyl)-piperidine-1-yl]-propyl}carboxamido-6-(3,5-difluorophenyl)-pyrimidine dihydrochloride.

A mixture of

1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methoxymethyl-1-(4-nitrophenyloxy)carbonyl-6-(3,5-difluorophenyl)pyrimidine (25 mg, 0.050 mmol) and 3-[4-(4-chloro-phenyl)-4-(5-fluoro-2-methoxy-phenyl)-piperidin-1-yl]-propylamine (23 mg, 0.060 mmol) in  $\text{CH}_2\text{Cl}_2$  ( 3 ml ) was stirred at room temperature for 12 hours. HCl solution (6 N, 2 ml) was added. The reaction mixture was stirred at room temperature for 6 hour. KOH solution (1 N) was added to neutralize the reaction mixture, and extracted with  $\text{CH}_2\text{Cl}_2$ . The extracts were dried ( $\text{Na}_2\text{SO}_4$ ), concentrated and chromatographed on prep. TLC (  $\text{CH}_2\text{Cl}_2$  :  $\text{CH}_3\text{OH}$  : 2 N  $\text{NH}_3$  in  $\text{CH}_3\text{OH}$  = 40:2:1) to give the title compound (18 mg, 50%) as a colorless oil. The hydrochloride of the title compound was synthesized using HCl in ether. Anal. Calculated for  $\text{C}_{36}\text{H}_{38}\text{ClN}_4\text{O}_6\text{F}_3$  + 1.0 HCl + 0.5  $\text{CHCl}_3$ : C, 54.45%; H, 4.68%; N, 6.36%. Found: C, 54.04%; H, 4.91%; N, 6.91%.

**Example 68:**

(+)-1-(5-(4-Cyano-4-phenylpiperidin-1-yl)-4(S)-methyl)pentyl-6-(3,4-difluorophenyl)-1,6-dihydro-5-(methoxycarbonyl)-4-methyl-2-pyrimidine.

a) (+)-1-(5-Bromo-4(S)-methyl)pentyl-6-(3,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-4-methyl-2-pyrimidone.

To a suspension of NaH (18 mg, 60% dispersion in mineral oil, 0.45 mmol.) in THF (5 mL) was added a solution of (+)-6-(3,4-difluorophenyl)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-pyrimidine (0.12 g, 0.4 mmol.) and HMPA (0.07 mL, 0.4 mmol.) in THF (15 mL) at 0°C. After 20 min, 2(S)-methyl-1,5-



dibromopentane (0.2 mg, 0.82 mmol.) was added. The reaction mixture was then refluxed for 2 h and quenched by water. It was partitioned between ethyl acetate and water. The organic layer was separated, treated with 6N HCl (5 mL) solution and stirred at room temperature for 1 h. The organic layer was then separated and dried over Na<sub>2</sub>SO<sub>4</sub>. After the removal of solvent, the residue was flash chromatographed over silica gel (eluent: 1:1 hexane/ethyl acetate) to give the product in 81% yield (0.15 g) as a yellow oil.

**b) (+)-1-(5-(4-Cyano-4-phenylpiperidin-1-yl)-4(S)-methyl)pentyl-6-(3,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-4-methyl-2-pyrimidone.**

A mixture of (+)-1-(5-Bromo-4(S)-methyl)pentyl-6-(3,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-4-methyl-2-pyrimidone (0.138g, 0.31 mmol.), 4-cyano-4-phenylpiperidine hydrochloride (0.138 g, 0.62 mmol.), potassium carbonate (0.22 g, 1.6 mmol.), sodium iodide (47 mg, 0.31 mmol.) and dioxane (8 mL) was refluxed overnight. The undissolved solid was then filtered off and the solvent was evaporated. The residue was purified by flash chromatographed over silica gel (eluent: ethyl acetate) to give the product in 18% yield (0.030 g) as a yellow oil.

Treatment of the free base with one equivalent of 1M HCl in ether gave the HCl salt as a light yellow solid: mp 133-135°C;  $[\alpha]_D = 87.4$  (1.75 mg/mL, MeOH). Anal. Calc. for C<sub>31</sub>H<sub>36</sub>F<sub>2</sub>N<sub>4</sub>O<sub>3</sub>.HCl.0.3CHCl<sub>3</sub>: C, 60.35; H, 6.04; N, 8.99. Found: C, 60.26; H, 6.29; N, 8.67.

**Example 69:**

**(+)-1-(5-(4-(2-Aminocarbonyl)phenyl)piperazin-1-yl)-4(S)-methyl)pentyl-6-(3,4-difluorophenyl)-1,6-dihydro-5-methoxy-carbonyl-4-methyl-2-pyrimidone.**

A mixture 1-(5-bromo-4(S)-methyl)pentyl-6-(3,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-4-methyl-2-pyrimidone (0.1g, 0.22 mmol.), 4-(2-aminocarbonylphenyl)piperazine (0.070 g, 0.34 mmol.),

potassium carbonate (0.16 g, 1.2 mmol.), sodium iodide (33 mg, 0.22 mmol.) and dioxane (8 mL) was refluxed overnight. The undissolved solid was then filtered off and the solvent was evaporated. The residue was purified by flash chromatographed over silica gel (eluent: 20:1 ethyl acetate/2M ammonia in methanol) to give the product in 41% yield (0.052 g) as a yellow oil. Treatment of the free base with one equivalent of 1M HCl in ether gave the HCl salt as a pale yellow solid: mp 168-171°C;  $[\alpha]_D = 83.5$  (2 mg/mL, MeOH). Anal. Calc. for  $C_{30}H_{37}F_2N_5O_4 \cdot 2HCl \cdot 0.5CH_2Cl_2$ : C, 53.48; H, 5.89; N, 10.22. Found: C, 53.74; H, 5.94; N, 9.99.

**Example 70:**

**1-(5-(4-Cyano-4-phenyl)piperidin-1-yl)pentyl-6-(3,4-difluoro-phenyl)-1,6-dihydro-5-methoxycarbonyl-2-methoxymethyl-4-methyl-pyrimidine.**

**a) 6-(3,4-Difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2-methoxy-methyl-4-methylpyrimidine.**

To a solution of 2-methoxyacetamidine hydrochloride (1.4 g, 11.2 mmol.) in DMF (6 mL) were added a solution of potassium *tert*-butoxide (0.69 g, 6.1 mmol.) in DMF (6 mL) and a solution of methyl {2-(3,4-difluorophenyl) methylene}-3-oxobutanoate (1.4 g, 5.8 mmol.) in DMF (6 mL) at 0°C. After the mixture was stirred for 0.5 hr at 0°C, *p*-toluenesulfonic acid monohydrate (2.2 g, 11.6 mmol.) was added. The mixture was heated at 100-120°C for 2.5 hrs. The mixture was cooled to room temperature, quenched with aqueous NaOH solution (2N, 30 mL), and extracted with ether. The organic layer was dried over  $Na_2SO_4$  and evaporated. The residue was flash chromatographed over silica gel (eluent: ethyl acetate) to give the product in 44% yield (0.8 g) as a yellow oil.

**b) 1-(5-Bromopentyl)-6-(3,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2-methoxymethyl-4-methylpyrimidine.**

To a suspension of NaH (0.11 g, 60% dispersion in mineral oil, 2.8 mmol.) in THF (20 mL) was added a solution of 6-(3,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2-methoxymethyl-4-methylpyrimidine (0.8 g, 2.6 mmol.) in THF (5 mL) at 0°C. After 20 min, 1,5-dibromopentane (0.7 mL, 5.2 mmol.) was added. The mixture was then refluxed overnight. After the removal of solvent, the residue was flash chromatographed over silica gel (eluent: ethyl acetate) to give the product in quantitative yield (1.2 g) as a yellow oil.

c) 1-(5-(4-Cyano-4-phenyl)piperidin-1-yl)pentyl-6-(3,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2-methoxymethyl-4-methylpyrimidine.

A mixture of 1-(5-bromopentyl)-6-(3,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2-methoxymethyl-4-methylpyrimidine (0.15 g, 0.33 mmol.), 4-cyano-4-phenylpiperidine hydrochloride (0.15 g, 0.67 mmol.), potassium carbonate (0.23 g, 1.7 mmol.), sodium iodide (50 mg, 0.33 mmol.) and acetone (6 mL) was refluxed overnight. The undissolved solid was then filtered off and the solvent was evaporated. The residue was flash chromatographed over silica gel (eluent: 10:1 ethyl acetate/2M ammonia in methanol) to give the title compound in 44% yield (0.080 g) as a yellow oil. Treatment of the free base with 2 equivalents of 1M HCl in ether gave the HCl salt as an off-white solid: mp 98-101°C. Anal. Calc. for  $C_{32}H_{38}F_2N_4O_3 \cdot 2HCl \cdot 1.1CHCl_3$ : C, 51.70; H, 5.39; N, 7.29. Found: C, 51.56; H, 5.52; N, 7.27.

**Example 71:**

(+)-6-(3,4-Difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2,4-dimethyl-1-(4(S)-methyl-5-(4-(2-methylphenyl)-4-(4-methyl-phenyl)piperidin-1-yl)pentyl)pyrimidine.

a) (+)-1-(5-Bromo-4(S)-methylpentyl)-6-(3,4-

**difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2,4-dimethylpyrimidine.**

To a suspension of NaH (47 mg, 60% dispersion in mineral oil, 1.17 mmol.) in THF (3 mL) was added a solution of 6-(3,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2,4-dimethyl-pyrimidine (0.3 g, 1.07 mmol.) and HMPA (0.193 g, 1.07 mmol.) in THF (4 mL) at 0°C. After 10 min, a solution of (-)-2-methyl-1,5-dibromopentane (0.86 g, 3.53 mmol.) in THF (5 mL) was added. The reaction mixture was then refluxed for 10 min. The solid formed was filtered off. After the removal of solvent, the residue was flash chromatographed over silica gel (eluent: 20:1 ethyl acetate/2M ammonia in methanol) to give the product in 36% yield (0.169 g) as a yellow oil. Chiral HPLC separation of the above diastereomers (Column: Chiralcel OD 20 x 250 mm. Eluent: 2-propanol/hexane/diethylamine 10:90:0.1) gave the desired enantiomer:  $[\alpha]_D = 200.9$  (25.5 mg/mL, CH<sub>2</sub>Cl<sub>2</sub>).

**b) (+)-6-(3,4-Difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2,4-dimethyl-1-(4(S)-methyl-5-(4-(2-methylphenyl)-4-(4-methyl-phenyl)piperidin-1-yl)pentyl)pyrimidine.**

A mixture of (+)-1-(5-bromo-4(S)-methylpentyl)-6-(3,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2,4-dimethyl-pyrimidine (0.1 g, 0.23 mmol.), 4-(2-methylphenyl)-4-(4-methylphenyl)piperidine hydrochloride (0.08 g, 0.26 mmol.), potassium carbonate (0.18 g, 1.3 mmol.), sodium iodide (0.033 g, 0.26 mmol.) and acetone (8 mL) was refluxed overnight. The undissolved solid was then filtered off and the solvent was evaporated. The residue was flash chromatographed over silica gel (eluent: 10:1 ethyl acetate/2M ammonia in methanol) to give the title compound in 64% yield (0.090 g) as a yellow oil. Treatment of the free base with 2 equivalents of 1M HCl in ether gave the HCl salt as a light

yellow solid: mp 130-133°C;  $[\alpha]_D = 62.4$  (1.85 mg/mL, MeOH). Anal. Calc. for  $C_{39}H_{47}F_2N_3O_2 \cdot 2HCl \cdot 2H_2O \cdot 0.65CHCl_3$ : C, 58.48; H, 5.64; N, 5.16. Found: C, 58.27; H, 6.46; N, 5.40.

5 **Example 72:**

**(+)-6-(3,4-Difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2-methoxymethyl-4-methyl-1-(5-(4-(2-methylphenyl)-4-(4-methyl-phenyl)piperidin-1-yl)pentyl)pyrimidine.**

- 10 a) **(+)-1-(5-Bromopentyl)-6-(3,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2-methoxymethyl-4-methylpyrimidine.**

To a suspension of NaH (0.11 g, 60% dispersion in mineral oil, 2.8 mmol.) in THF (20 mL) was added a  
15 solution of 6-(3,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2-methoxymethyl-4-methylpyrimidine (0.8 g, 2.6 mmol.) in THF (5 mL) at 0°C. After 20 min., 1,5-dibromopentane (0.7 mL, 5.2 mmol.) was added. The mixture was then refluxed overnight. After  
20 the removal of the solvent, the residue was flash chromatographed over silica gel (eluent: ethyl acetate) to give the product in quantitative yield (1.2 g) as a yellow oil. Chiral HPLC separation (Column: Chiralcel OD 20 x 250 mm. Eluent: 2-  
25 propanol/hexane/diethylamine 10:90:0.1) gave the title enantiomer:  $[\alpha]_D = 190.5$  (55 mg/mL,  $CH_2Cl_2$ ).

- b) (+)-6-(3,4-Difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2-methoxymethyl-4-methyl-1-(5-(4-(2-methylphenyl)-4-(4-methyl-phenyl)piperidin-1-yl)pentyl)pyrimidine.**

A mixture of (+)-1-(5-bromopentyl)-6-(3,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2-methoxymethyl-4-methylpyrimidine (0.08 g, 0.17  
35 mmol.), 4-(2-methylphenyl)-4-(4-methylphenyl)piperidine hydrochloride (0.063 g, 0.21 mmol.), potassium carbonate (0.14 g, 1.0 mmol.), sodium iodide (26 mg, 0.17 mmol.) and acetone (6 mL)

was refluxed overnight. The undissolved solid was then filtered off and the solvent was evaporated. The residue was flash chromatographed over silica gel (eluent: 10:1 ethyl acetate/2M ammonia in methanol) to give the title compound in 89% yield (0.1 g) as a yellow oil. Treatment of the free base with 2 equivalents of 1M HCl in ether gave the HCl salt as a pale yellow solid: mp 137-140°C;  $[\alpha]_D = 56.5$  (1.65 mg/mL, MeOH). Anal. Calc. for

$C_{39}H_{47}F_2N_3O_3 \cdot 2HCl \cdot 2H_2O \cdot 0.75CHCl_3$ : C, 56.68; H, 6.43; N, 4.99. Found: C, 56.55; H, 6.19; N, 5.02.

**Example 73:**

**(+)-1,2,3,6-Tetrahydro-1-{N-[3-(4,4-diphenylpiperidin-1-yl)-**

**propyl]}carboxamido-5-methoxycarbonyl-2-oxo-6-(3,4-difluoro-phenyl)-4-methoxymethylpyrimidine hydrochloride.**

A solution of (+)-6-(3,4-difluorophenyl)-1,2,3,6-tetrahydro-2-oxo-5-methoxycarbonyl-4-methoxymethyl-1-(4-nitrophenoxy)-carbonylpyrimidine (0.160 g) and 3-(4,4-diphenyl-piperidin-1-yl)propylamine (0.150 g) in tetrahydrofuran (10 mL) was stirred at room temperature for 14 hours. The product was purified by preparative thin layer chromatography on silica gel using ethyl acetate as eluent to give 0.22 g of the product as a syrup, which was converted to the hydrochloride salt by treatment with 1N HCl in ether; m.p. 178-181 °C;  $[\alpha]_D = +99.6$  (c = 0.24, MeOH). Anal. Calcd. for  $C_{35}H_{39}ClF_2N_4O_5 \cdot 0.2CH_2Cl_2$ : C, 60.93; H, 5.74; N, 8.06. Found: C, 60.73; H, 5.89; N, 7.92.

**Example 74:**

**(±)-1,2,3,6-Tetrahydro-1-{N-[3-(4,4-diphenylpiperidin-1-yl)-**

**propyl]}carboxamido-5-acetyl-2-oxo-6-(3,4,5-trifluorophenyl)-4-methylpyrimidine dihydrochloride.**

A mixture of 6-(3,4,5-difluorophenyl)-1,2,3,6-tetrahydro-2-oxo-

5-acetyl-4-methyl-1-[(4-nitrophenoxy)carbonyl]pyrimidine (0.150 g) and 3-(4,4-diphenylpiperidin-1-yl)propylamine (0.180 g) in THF (10 mL) was stirred at room temperature for 14 h. The product was purified by preparative thin layer chromatography on silica gel using ethyl acetate as eluent to give 0.23 g of the product as a syrup, which was converted to the hydrochloride salt by treatment with 1N HCl in ether; m.p. 180-182 °C.

Anal. Calcd. for  $C_{34}H_{36}ClF_3N_4O_3 \cdot 1CH_2Cl_2$ : C, 57.90; H, 5.28; N, 7.72. Found: C, 57.54; H, 5.10; N, 7.79.

**Example 75:**

(±)-1,2,3,6-Tetrahydro-1-{N-[3-(4-(2-methylphenyl)-4-methylphenyl)piperidin-1-yl]-propyl}carboxamido-5-acetyl-2-oxo-6-(3,4,5-trifluorophenyl)-4-methylpyrimidine hydrochloride.

A mixture of 6-(3,4,5-difluorophenyl)-1,2,3,6-tetrahydro-2-oxo-5-acetyl-4-methyl-1-[(4-nitrophenoxy)carbonyl]pyrimidine (0.02 g) and 3-[4-(2-methylphenyl)-4-(4-methylphenyl)-piperidin-1-yl]-propylamine (0.02 g) in THF (1 mL) was stirred at room temperature for 14 h. The product was purified by preparative thinlayer chromatography on silica gel using ethyl acetate as eluent to give 0.03 g of the product as a syrup, which was converted to the hydrochloride salt by treatment with 1N HCl in ether; m.p. 180-184 °C.

Anal. Calcd. for  $C_{36}H_{40}ClF_3N_4O_3 \cdot 0.4CH_2Cl_2$ : C, 62.18; H, 5.85; N, 7.97. Found: C, 62.42; H, 6.00; N, 7.88.

**Example 76:**

(+)-6-(3,4-Difluorophenyl)-1-[{N-[4-cyano-4-phenylpiperidin-1-yl]-2,2-difluoropropyl}carboxamido]-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1,2,3,6-tetrahydro-pyrimidine.

a) 3-[4-Cyano-4-phenyl-piperidin-1-yl] (2-

**hydroxypropyl)-phthalimide.**

A mixture of 4-cyano-4-phenylpiperidine (10 g, 44.9 mmol) and 2,3-epoxypropylphthalimide (10.94 g, 53.9 mmol) in DMF (100 mL) was stirred and heated at 70 °C for 72 h. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel using chloroform-methanol-2M ammonia in methanol (1000/28/14) as the eluent, to obtain the desired product as a viscous oil (16.45 g, 86%).

**b) 3-[4-Cyano-4-phenyl-piperidin-1-yl](2-oxopropyl)phthalimide.**

To a stirred solution of DMSO (3.6 mL, 51.07 mmol) in dichloromethane (100 mL) at -78 °C, oxalyl chloride (2.18 mL, 24.5 mmol) in dichloromethane (15 mL) was added and the mixture was stirred for 3 min. To this, a solution of 3-[4-cyano-4-phenyl-piperidin-1-yl](2-hydroxypropyl)phthalimide (8.70 g, 20.42 mmol) in dichloromethane (25 mL) was added and the stirring was continued for 15 min. It was warmed to room temperature and added 5 mL of water. The pH of the mixture was adjusted to 10-11 by adding 1N NaOH and the dichloromethane layer was separated. The aqueous layer was extracted with more dichloromethane (3 X 100 mL). The combined dichloromethane extracts were dried (magnesium sulfate), solvents evaporated, and the residue was purified by flash chromatography on silica gel using ethyl acetate/hexane as eluent (6.05 g, 70%).

**c) 3-[4-Cyano-4-phenyl-piperidin-1-yl](2,2-difluoropropyl)-phthalimide.**

To a well stirred solution of 3-[4-cyano-4-phenyl-piperidin-1-yl](2-oxopropyl)phthalimide (0.22 g, 0.52 mmol) in anhydrous dichloromethane (25 mL) at -78°C, under argon atmosphere was added diethyaminosulfur trifluoride (DAST) (0.251 mg, 1.56 mmol) and the mixture was allowed to warm to room



temperature. After 36 h, the reaction mixture was cooled to 0-5 °C and to this saturated sodium bicarbonate solution (20 mL) was added cautiously. The dichloromethane layer was separated, dried (sodium sulfate), and the solvent was evaporated. The product was purified by flash column chromatography on silica gel using 30% ethyl acetate in hexanes as eluent (80 mg, 38%). <sup>1</sup>H-NMR was in agreement with the product.

**d) 3-[4-Cyano-4-phenylpiperidin-1-yl](2,2-difluoro)propylamine.**

A mixture of 3-[4-cyano-4-phenyl-piperidin-1-yl](2,2-difluoro-propyl)phthalimide (120 mg, 0.29 mmol) and hydrazine (0.5 mL g) in methanol (15 mL) was stirred and refluxed for 4.5 h. It was cooled, filtered, and the solid was washed with methanol (30 mL).

Evaporation of solvent from the filtrate gave the product as a viscous oil (60 mg, 73%) which was used in the next step without any further purification.

**e) (+)-6-(3,4-Difluorophenyl-1-[(N-[4-cyano-4-phenylpiperidin-1-yl]-2,2-difluoropropyl)-carboxamido]-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1,2,3,6-tetrahydro-pyrimidine.**

A solution of (+)-5-methoxycarbonyl-4-methoxymethyl-1,2,3,6-tetrahydro-2-oxo-6-(3,4-difluorophenyl)-1-[(4-nitrophenoxy)-carbonyl]pyrimidine (38 mg, 0.077 mmol) and 3-[4-cyano-4-phenyl-piperidin-1-yl](2,2-difluoropropyl)propylamine (30 mg, 0.107 mmol) in dichloromethane (3 mL) was stirred at room

temperature for 12 hours. The mixture was purified by preparative tlc on silica gel (60% ethyl acetate in hexanes) to give 38 mg (81%) as a white powder. The HCl salt was prepared by treatment of a solution of the free base in ether with 1N HCl in ether. The white powder was dried and recrystallized from anhydrous 2-propanol. M.P. 184-186 °C; [ $\alpha$ ]<sub>D</sub> = +96.36 (c = 0.55, dichloromethane). Anal. Calcd. for

$C_{30}H_{32}N_5O_5F_4Cl$ :C, 55.12; H, 4.87; N, 9.95. Found: C, 55.09; H, 4.93; N, 9.71.

**Example 77:**

5 (+)-1,2,3,6-Tetrahydro-1-{N-[4-(4-methoxycarbonyl-4-phenyl-  
piperidin-1-yl)-piperidinyl]}carbonyl-5-methoxycarbon  
yl-2-  
oxo-6-(3,4,5-trifluorophenyl)-4-methoxymethylpyrimidi  
ne hydrochloride.

10 a) 1-Benzyl-4-(4-Methoxycarbonyl-4-phenylpiperidin-1-yl)-piperidine.

A mixture of 4-methoxycarbonyl-4-phenylpiperidine (6.50 g, 0.0296 mol), N-benzyl-4-piperidone (5.62 g), and p-toluenesulfonic acid (100 mg) in benzene (100  
15 mL) was heated at 110 °C for 14 h with a Dean-Stark trap to remove the water that formed. Solvent was evaporated and the residue was redissolved in methanol (20 mL). To this, sodium cyanoborohydride (1.86 g) was added in portions and the mixture was  
20 stirred at room temperature for 6 h. Solvent was evaporated, the residue was mixed with 1N NaOH (10 mL) and the resultant mixture was extracted with ether (4 X 20 mL). The combined extracts were washed with brine (20 mL), dried (sodium sulfate), and the  
25 solvent evaporated. The residue was purified by column chromatography on silica gel using dichloromethane/methanol/2M ammonia in methanol (50/20/10) as eluent. The product was obtained as a viscous oil (8.5 g), which on trituration with hexane became a  
30 white powder.

b) 4-(4-Methoxycarbonyl-4-phenylpiperidin-1-yl)-piperidine.

A mixture of 1-benzyl-4-(4-Methoxycarbonyl-4-phenylpiperidin-1-yl)piperidine (3.92 g) and 10% Pd-C  
35 (0.4 g) in ethanol (200 mL) was hydrogenated at 80 psi for 12h. The catalyst was removed by filtration and the solvent was evaporated from the filtrate to

leave the product (2.9 g, 96%) as a white powder.

c) (+)-1,2,3,6-Tetrahydro-1-{N-[4-(4-methoxycarbonyl-4-phenyl-piperidin-1-yl)-piperidinyl]}carbonyl-5-methoxycarbonyl-2-oxo-6-(3,4,5-trifluorophenyl)-4-methoxymethylpyrimidine hydrochloride.

A solution of (+)-6-(3,4,5-trifluorophenyl)-1,2,3,6-tetrahydro-2-oxo-5-methoxycarbonyl-4-methoxymethyl-1-(4-nitrophenoxy)-carbonylpyrimidine (50 mg, prepared similarly to (+)-6-(3,4-difluorophenyl)-1,2,3,6-tetrahydro-2-oxo-5-methoxycarbonyl-4-methoxy-methyl-1-(4-nitrophenoxy)carbonylpyrimidine) and 4-(4-methoxycarbonyl-4-phenylpiperidin-1-yl)piperidine (50 mg) in THF (2 mL) was stirred at room temperature for 14 hours. The product was purified by preparative thin layer chromatography on silica gel using ethyl acetate as eluent to give 70 mg of the product as a syrup, which was converted to the hydrochloride salt by treatment with 1N HCl in ether; m.p. 178-181 °C;  $[\alpha]_D = +135$  (c = 0.65, MeOH). Anal. Calcd. for  $C_{35}H_{38}ClF_3N_4O_7 \cdot 0.4CH_2Cl_2$ : C, 55.02; H, 5.36; N, 7.68. Found: C, 55.22; H, 5.48; N, 7.56.

**Example 78:**

(+)-1,2,3,6-Tetrahydro-1-{N-[2-(4-phenyl-4-methoxycarbonyl)-piperidin-1-yl)ethyl]}acetamido-5-methoxycarbonyl-2-oxo-6-(3,4-difluorophenyl)-4-methylpyrimidine hydrochloride.

a)

(+)-1,2,3,6-Tetrahydro-1-{bezyloxycarbonylmethyl)-5-methoxy-carbonyl-2-oxo-6-(3,4-difluorophenyl)-4-methylpyrimidine.

A mixture of (+)-1,6-dihydro-5-methoxycarbonyl-2-methoxy-6-(3,4-difluorophenyl)-4-methylpyrimidine (0.296 g),

- benzyl bromoacetate (0.229 g), potassium carbonate (0.600 g), and potassium iodide (30 mg) in acetone (20 mL) was heated under reflux for 14 h. It was filtered, washed with acetone (15 mL). To the combined filtrates 6N HCl (0.5 mL) was added and stirred for 4 h. Solvent was evaporated and the product was purified by preparative thin layer chromatography on silica gel using hexane/ethyl acetate (1:1) to give the product as a foam (0.20 g) which was used in the next step without further characterization.
- 5 b) (+)-1,2,3,6-Tetrahydro-5-methoxycarbonyl-2-oxo-6-(3,4-difluorophenyl)-4-methylpyrimidine-1-acetic acid.
- 10 To a suspension of 10% Pd-C (20 mg) in MeOH (10 mL) and H<sub>2</sub>O (2 mL) was added a solution of (+)-1,2,3,6-tetrahydro-1-(benzyloxy-carbonylmethyl)-5-methoxycarbonyl-2-oxo-6-(3,4-difluorophenyl)-4-methylpyrimidine (200 mg) in methanol (1 mL) and the mixture was hydrogenated at 80 psi for 4 h. The black suspension was filtered through a pad of Celite and washed thoroughly with MeOH (100 mL). Solvent was evaporated from the combined filtrate to yield the product (+)-1,2,3,6-tetrahydro-1-5-methoxycarbonyl-2-oxo-6-(3,4-difluorophenyl)-4-methylpyrimidine-1-acetic acid as a white solid (0.15 g). It was used in the next step without further purification.
- 15 20 25 30 c) (+)-1,2,3,6-Tetrahydro-1-{N-[2-(4-phenyl-4-methoxycarbonyl)-piperidin-1-yl)ethyl]}acetamido-5-methoxycarbonyl-2-oxo-6-(3,4-difluorophenyl)-4-methylpyrimidine hydrochloride.
- 35 A mixture of (+)-1,2,3,6-tetrahydro-1-5-methoxycarbonyl-2-oxo-6-(3,4-difluorophenyl)-4-methylpyrimidine-1-acetic acid (20 mg), 2-(4-phenyl-4-

- methoxycarbonyl)piperidin-1-yl)ethylamine (20 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (20 mg), and 4-(N,N-dimethylamino)pyridine (20 mg) in anhydrous
- 5 dichloromethane (4 mL) was stirred at room temperature for 12 h. The reaction mixture was purified by preparative thin layer chromatography on silica gel using ethyl acetate as the eluent. The product was dissolved in ether (0.5 mL), cooled to 0-
- 10 5 °C and treated with 1N HCl in ether (10 mL) and the solvents evaporated to leave the product as a white powder (25 mg); mp 247-250°C;  $[\alpha]_D = +108.2$  (c = 0.50, MeOH). Anal. Calcd. for  $C_{30}H_{35}N_4O_6F_2Cl$ : C, 58.02; H, 5.68; N, 9.02. Found: C, 58.21; H, 5.70; N, 8.92.
- 15 **Example 79:**  
**1,6-Dihydro-1-{N-[2-(4-phenyl-4-methoxycarbonyl)piperidin-1-yl)-ethyl]}acetamido-5-methoxycarbonyl-6-(3,4,5-trifluorophenyl)-2,4-dimethylpyrimidine dihydrochloride.**
- 20 **a) 6-(3,4,5-trifluorophenyl)-1,6-dihydro-5-methoxycarbonyl-2,4-dimethylpyrimidine.**  
To a solution of acetamidine hydrochloride (1.41 g, 14.9 mmol.) in DMF (10 mL) was added a solution of potassium *tert*-butoxide (12 mL, 1.0 M in THF) at 0°C.
- 25 After stirred for 10 minutes, a solution of methyl {2-(3,4,5-trifluorophenyl)methylene}-3-oxobutanoate (2.10 g, 10.0 mmol) in DMF (10 mL) was added and the mixture was stirred for 2 hours while warmed up to room temperature. *p*-Toluenesulfonic acid monohydrate
- 30 (4.50 g, 23.6 mmol) was added to the solution and the reaction mixture was heated at 110-120 °C for 2 hours. The mixture was cooled to room temperature and poured into ice (100 g) and aqueous NaOH solution (3 N, 200 mL), and extracted with ether (3x100 mL). The organic
- 35 layers were combined, dried ( $K_2CO_3$ ) and evaporated. The residue was purified by flash chromatography over silica gel (eluent: 10-15% MeOH in methylene

chloride) to afford the product in 47% yield ( 1.4 g ) as an oil.

**b) 1,6-Dihydro-1-{bezyloxycarbonylmethyl}-5-methoxycarbonyl-**

5     **6-(3,4,5-trifluorophenyl)-2,4-dimethylpyrimidine.** A mixture of 1,6-dihydro-5-methoxycarbonyl-6-(3,4,5-trifluorophenyl)-2,4-dimethylpyrimidine (0.298 g), benzyl bromoacetate (0.229 g), potassium carbonate (0.600 g), and  
10     potassium iodide (30 mg) in acetone (20 mL) was heated under reflux for 14 h. It was filtered, washed with acetone (15 mL). Solvent was evaporated and the product was purified by preparative thin  
15     layer chromatography on silica gel using hexane/ethyl acetate (1:1) to give the product as a foam (0.34 g). NMR confirmed it to be the desired product which was used in the next step without any further characterization.

**c) 1,6-Dihydro-5-**

20     **methoxycarbonyl-6-(3,4,5-trifluorophenyl)-2,4-dimethylpyrimidine-1-acetic acid.** To a suspension of 10% Pd-C (30 mg) in MeOH (10 mL) and H<sub>2</sub>O (2 mL) was added a solution of  
25     1,6-dihydro-1-{bezyloxycarbonylmethyl}-5-methoxycarbonyl-6-(3,4,5-trifluorophenyl)-2,4-dimethylpyrimidine (300 mg) in methanol (1 mL) and the mixture was hydrogenated at 80 psi for 4 h. The black suspension was filtered through a pad of Celite and washed  
30     thoroughly with MeOH (100 mL). Solvent was evaporated from the combined filtrate to leave the product 1,6-dihydro-5-methoxycarbonyl-6-(3,4,5-trifluorophenyl)-2,4-dimethylpyrimidine-1-acetic acid as a white solid (0.225 g).  
35     It was used in the next step without further purification.

**d) 1,6-Dihydro-1-{N-[2-(4-phenyl-4-**

methoxycarbonyl)piperidin-1-yl)ethyl]}acetamido-5-methoxycarbonyl-6-(3,4,5-trifluoro-phenyl)-2,4-dimethylpyrimidine dihydrochloride.

- 5 A mixture of 1,6-dihydro-5-methoxycarbonyl-6-(3,4,5-trifluoro-phenyl)-2,4-dimethylpyrimidine-1-acetic acid (20 mg), 2-(4-phenyl-4-methoxycarbonyl)piperidin-1-yl)ethylamine (20 mg), 1-(3-dimethyl-aminopropyl)-3-ethylcarbodiimide hydrochloride (20 mg), and 4-(N,N-dimethylamino)pyridine (20 mg) in anhydrous  
10 dichloromethane (4 mL) was stirred at room temperature for 12 h. The reaction mixture was purified by preparative thin layer chromatography on silica gel using ethyl acetate as the eluent. The  
15 product was dissolved in ether (0.5 mL), cooled to 0-5 °C and treated with 1N HCl in ether (10 mL) and the solvents evaporated to leave the product as a white powder (25 mg); m.p. 187-190 °C; Anal. Calcd. for  $C_{31}H_{37}N_4O_5F_3Cl_2$ : C, 55.28; H, 5.54; N, 8.32. Found: C, 55.36; H, 5.80; N, 8.41.

**Example 80:**

(+)-1,2,3,6-Tetrahydro-1-{N-[4-(2-nitrophenyl)piperazin-1-yl]-propyl}-carboxamido-4-methyl-6-(3,4-difluorophenyl)-2-oxo-pyrimidine.

**25 a) 1-(2-nitrophenyl)-piperazine.**

- A heterogenous reaction mixture containing 2-bromo-1-nitrobenzene (2.02 g, 10.0 mmol) and piperazine (4.3 g, 50.0 mmol) was heated at 100°C for 10 h. The orange-red solid was extracted with ethyl acetate and  
30 washed thoroughly with 3 N NaOH solution followed by brine. The organic layer was separated and dried over  $Na_2SO_4$ , filtered and the solvent was removed in vacuo. The resulting red oil was purified by column chromatography on silica gel (1:1 hexane/EtOAc  
35 followed by 4:1 EtOAc/MeOH) to yield 1-(2-nitrophenyl)-piperazine as an orange-red oil (1.90 g, 92%). It was converted to its hydrochloride salt.

Anal. calcd. for  $C_{10}H_{14}N_3O_2Cl \cdot 0.10 CHCl_3$ : C, 47.46; H, 5.56; N, 16.44. Found: C, 47.63; H, 5.69; N, 16.42.

**b) (+)-1,2,3,6-Tetrahydro-1-{N-[4-(2-nitrophenyl)piperazin-1-yl]propyl}-carboxamido-4-methyl-6-(3,4-difluorophenyl)-2-oxo-pyrimidine.**

To a solution of (+)-1-(3-bromo-propylcarbamoyl)-6-(3,4-difluoro-phenyl)-4-methyl-2-oxo-1,6-dihydro-pyrimidine-5-carboxylic acid methyl ester (0.22 g, 0.5 mmol) and 1-(2-nitro-phenyl)-piperazine (0.15 g, 0.75 mmol) in 20 mL of anhydrous acetone was added powdered  $K_2CO_3$  (0.34 g, 3.5 mmol) and KI (0.07 g, 0.5 mmol) and the resulting suspension was heated to reflux for 10 h. The suspension was cooled, filtered and the solvent was evaporated and the residue was purified by column chromatography on silica gel with EtOAc/MeOH (5:1) as the eluting system. (+)-1,2,3,6-tetrahydro-1-{N-4-(2-nitrophenyl)piperazin-1-yl}propyl}-carboxamido-4-methyl-6-(3,4-difluorophenyl)-2-oxo-pyrimidine was obtained as a yellow oil (0.08 g, 29% yield). The product was analyzed as its hydrochloride salt. M.P. 133-136°C;  $[\alpha]_D = +56.7$  (c = 0.11, MeOH). Anal. calcd. for  $C_{27}H_{31}N_6F_2O_6Cl \cdot 0.20 CH_2Cl_2$ : C, 51.62; H, 4.97; N, 13.28. Found: C, 51.35; H, 5.18; N, 11.99.

**Example 81:**

**(+)-1,2,3,6-Tetrahydro-1-{N-[4-(2-amino-phenyl)piperazin-1-yl]propyl}-carboxamido-4-methyl-6-(3,4-difluorophenyl)-2-oxo-pyrimidine.**

To a cooled suspension of 10% palladium on carbon (40 mg) in methanol (25 mL) was added a solution of (+)-1,2,3,6-tetrahydro-1-{N-4-(2-nitrophenyl)piperazin-1-yl}propyl}-carboxamido-4-methyl-6-(3,4-difluorophenyl)-2-oxo-pyrimidine (50 mg, 0.09 mmol) in methanol (5 mL) and the resulting suspension was hydrogenated at 100 psi at room temperature for 3 h. The suspension was filtered through a pad of celite and washed with 50 mL of methanol. The solvent was



removed in vacuo from the combined filtrate to get 0.03 g (60%) of (+)-1,2,3,6-tetrahydro-1-{N-[4-(2-amino-phenyl)-piperazin-1-yl]propyl}-carboxamido-4-methyl-6-(3,4-difluoro-phenyl)-2-oxo-pyrimidine as a yellow oil. No purification was performed on this material and it was characterized as its dihydrochloride salt. Mass spectrum (low res.) 543 (M+1, 100%);  $[\alpha]_D = +75.1$  (c = 0.41, MeOH); Anal calcd. for  $C_{27}H_{34}N_6F_2O_4Cl_2 \cdot 0.03 CHCl_3$ : C, 52.48; H, 5.54; N, 13.59. Found: C, 52.35; H, 5.83; N, 12.50.

**Example 82:**

**1,2,3,6-Tetrahydro-1-{N-[4-(6-(nitro)pyrid-2-yl)piperazin-1-yl]propyl}-carboxamido-4-methyl-6-(3,4-difluorophenyl)-2-oxo-pyrimidine.**

**a) 1-[6-(nitro)pyrid-2-yl]piperazine.**

To a solution of 2-chloro-3-nitropyridine (1.58 g, 10.0 mmol) in 1,4-dioxane (50 mL) was added piperazine (4.3 g, 50.0 mmol) and powdered  $K_2CO_3$  (50.0 mmol, 6.9 g) and the resulting suspension was heated at reflux for 10 h. After the suspension was cooled, it was extracted with ethyl acetate (2 X 50 mL) and washed successively with 3 N NaOH (20 mL) and water (20 mL). The organic layer was dried over  $Na_2SO_4$ , filtered and the solvent was removed in vacuo. The resulting residue was purified by column chromatography on silica gel (1:1 hexane/EtOAc followed by 4:1 EtOAc/MeOH) to yield 1-[6-(nitro)pyrid-2-yl]piperazine as a yellow solid. It was characterized as a hydrochloride salt.

Anal calcd. for  $C_9H_{12}N_4O_2Cl \cdot 0.25 CHCl_3$ : C, 40.47; H, 4.86; N, 20.41. Found: C, 40.72; H, 4.97; N, 20.50.

**b) 1,2,3,6-Tetrahydro-1-{N-[4-(6-(nitro)pyrid-2-yl)piperazin-1-yl]propyl}-carboxamido-4-methyl-6-(3,4-difluorophenyl)-2-oxo-pyrimidine.**

To a solution of 1-(3-bromo-propylcarbonyl)-6-(3,4-difluoro-phenyl)-4-methyl-2-oxo-1,6-dihydro-

pyrimidine-5-carboxylic acid methyl ester (0.04 g, 0.1 mmol) and 1-[6-(nitro)pyrid-2-yl]-piperazine (0.03 g, 0.15 mmol) in 10 mL of anhydrous acetone was added powdered  $K_2CO_3$  (0.06 g, 0.6 mmol) and KI (0.01 g, 0.10 mmol) and the resulting suspension was heated to reflux for 10 h. The suspension was cooled, filtered and the solvent was evaporated in vacuo. The residue was purified by column chromatography on silica gel with EtOAc/MeOH (5:1) as the eluting system. 1,2,3,6-tetrahydro-1-{N-[4-(6-(nitro)pyrid-2-yl)-piperazin-1-yl]propyl}-carboxamido-4-methyl-6-(3,4-difluoro-phenyl)-2-oxo-pyrimidine was obtained as a yellow oil (0.04 g, 70% yield). The product was analyzed as its hydrochloride salt. M.P. 142-145°C; Anal calcd. for  $C_{26}H_{30}N_7F_2O_6Cl$  0.30  $CH_2Cl_2$ : C, 48.91; H, 4.74; N, 15.18. Found: C, 48.94; H, 4.94; N, 13.29.

**Example 83:**

**(+)-1,2,3,6-Tetrahydro-1-{N-[2-(S)-methyl]-4-(2-nitrophenyl)-piperazin-1-yl]propyl}-carboxamido-4-methyl-6-(3,4-difluoro-phenyl)-2-oxo-pyrimidine.**

**a) (S)-(+)-3-methyl-1-(2-nitrophenyl)piperazine.**

To a solution of 2-bromo-1-nitrobenzene (0.6 g, 3.0 mmol) in 1,4-dioxane (15 mL) was added (S)-(+)-2-methylpiperazine (0.5 g, 0.5 mmol) and powdered  $K_2CO_3$  (15.0 mmol, 1.5 g) and the resulting suspension was heated at reflux for 10 h. After the suspension was cooled, it was filtered through a sintered glass funnel and the solvent was evaporated in vacuo. The resulting residue was purified by column chromatography on silica gel (1:1 hexane/EtOAc followed by 4:1 EtOAc/MeOH) to yield (S)-(+)-3-methyl-1-(2-nitrophenyl)-piperazine as an orange oil (0.53 g, 80%).

**b) (+)-1,2,3,6-Tetrahydro-1-{N-[2-(S)-methyl]-4-(2-nitrophenyl)-piperazin-1-yl]propyl}-carboxamido-4-methyl-6-(3,4-difluoro)-phenyl-2-oxo-pyrimidine.**

To a solution of (+)-1-(3-bromopropylcarbonyl)-6-

(3,4-difluorophenyl)-4-methyl-2-oxo-1,6-dihydro-pyrimidine-5-carboxylic acid methyl ester (0.2 g, 0.5 mmol) and (S)-(+)-3-methyl-1-(2-nitrophenyl)piperazine (0.17 g, 0.75 mmol) in 20 mL of anhydrous acetone was added powdered  $K_2CO_3$  (0.34 g, 3.5 mmol) and KI (0.07 g, 0.5 mmol) and the resulting suspension was heated to reflux for 10 h. TLC indicated a new spot for the product ( $R_f$  = 0.3, 3:0.5 EtOAc/MeOH) and mostly the starting material. The suspension was cooled, filtered and the solvent was evaporated and the residue was purified by column chromatography on silica gel with EtOAc/MeOH (5:1) as the eluting system. (+)-1,2,3,6-Tetrahydro-1-{N-[2-(S)-methyl)-4-(2-nitrophenyl)piperazin-1-yl]propyl}-carboxamido-4-methyl-6-(3,4-difluorophenyl)-2-oxo-pyrimidine was obtained as yellow oil (0.03 g, 10% yield). The product was analyzed as its hydrochloride salt. M.P. 150-153°C;  $[\alpha]_D = 58.3$  (c = 0.3, MeOH); Anal calcd. for  $C_{28}H_{33}N_6F_2O_6Cl \cdot 0.20 CH_2Cl_2$ : C, 52.92; H, 5.26; N, 13.13. Found: C, 52.84; H, 5.68; N, 12.94.

**Example 84:**

A) (+)-1,2,3,6-Tetrahydro-5-methoxycarbonyl-4-methyl-2-oxo-1-{N-[2-(R)-methyl)-4-(2-nitrophenyl)piperazin-1-yl]propyl}-6-(3,4-difluorophenyl)pyrimidine.

a) (R)-(+)-3-methyl-1-(2-nitrophenyl)piperazine.

To a solution of 2-bromo-nitrobenzene (0.4 g, 2.0 mmol) in 1,4-dioxane (10 mL) was added (R)-(+)-2-methylpiperazine (0.25 g, 0.25 mmol) and powdered  $K_2CO_3$  (7.5 mmol, 0.8 g) and the resulting suspension was heated at reflux for 10 h. After the suspension was cooled, it was filtered through a sintered glass funnel and the solvent was evaporated in vacuo. The resulting residue was purified by column chromatography on silica gel (1:1 hexane/EtOAc followed by 4:1 EtOAc/MeOH) to yield (R)-(+)-3-

methyl-1-(2-nitrophenyl)-piperazine as an orange-red oil (0.26 g, 78%).

- 5      b) (+)-1,2,3,6-Tetrahydro-5-methoxycarbonyl-4-methyl-2-oxo-1-{N-[2-(R)-methyl]-4-(2-nitrophenyl)piperazin-1-yl}propyl}-6-(3,4-difluorophenyl)pyrimidine.

To a solution of (+)-1-(3-bromo-propylcarbamoyl)-6-(3,4-difluorophenyl)-4-methyl-2-oxo-1,6-dihydro-pyrimidine-5-carboxylic acid methyl ester (0.11 g, 0.25 mmol) and (R)-(+)-3-methyl-1-(2-nitrophenyl)-piperazine (0.11 g, 0.50 mmol) in 20 mL of anhydrous acetone was added powdered  $K_2CO_3$  (0.34 g, 3.5 mmol) and KI (0.07 g, 0.5 mmol) and the resulting suspension was heated to reflux for 10 h. TLC indicated a new spot for the product ( $R_f$  = 0.3, 3:0.5 EtOAc/MeOH) and mostly the starting material. The suspension was cooled, filtered and the solvent was evaporated and the residue was purified by column chromatography on silica gel with EtOAc/MeOH (5:1) as the eluting system. (+)-1,2,3,6-Tetrahydro-5-methoxycarbonyl-4-methyl-2-oxo-1-{N-[2-(R)-methyl]-4-(2-nitrophenyl)piperazin-1-yl}propyl}-6-(3,4-difluorophenyl)-pyrimidine was obtained as yellow oil (0.02 g, 14% yield). The product was analyzed as its hydrochloride salt. M.P. 135-138°C;  $[\alpha]_D = +63.5$  ( $c = 0.2$ , MeOH); Anal calcd. for  $C_{28}H_{33}N_6F_2O_6Cl \cdot 1.0 CHCl_3$ : C, 46.92; H, 4.62; N, 11.32. Found: C, 46.94; H, 4.97; N, 11.47.

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**Example 85:**

- 30      (+)-1,2,3,6-Tetrahydro-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1-{N-[4-(2-methoxy-5-methyl)phenyl]-4-phenyl-piperidin-1-yl}propyl}-6-(3,4-difluorophenyl) pyrimidine.

- a) 4-(2-Methoxy-5-methyl)phenyl-4-phenylpiperidine hydrochloride.

35      To a 100 mL round bottom flask equipped with a rubber septum and a stirring bar was added 4-hydroxy-4-phenyl-piperidine (1.25 g, 7.0 mmol) followed by 10

mL of 4-methylanisole. The resulting solution was stirred at room temperature under argon atmosphere and then  $\text{AlCl}_3$  (2.82 g, 21.0 mmol) was added in one portion. An exotherm was observed. The reaction mixture was stirred for 8 h and then poured carefully over 150 ml of ice-water. The white solid that precipitated out was filtered and washed thoroughly with water followed by diethyl ether to obtain 4-(2-methoxy-5-methyl)-phenyl-4-phenyl-piperidine hydrochloride (1.59 g, 50%) as a white solid. Mass spectrum: 282 ( $M+1$ , 100%). Anal calcd. for  $\text{C}_{19}\text{H}_{24}\text{NOCl} \cdot 0.15 \text{ CH}_2\text{Cl}_2$ : C, 69.57; H, 7.41; N, 4.24. Found: C, 69.62; H, 7.31; N, 4.36.

**b) 3-[4-(2-methoxy-5-methyl)phenyl-4-phenyl-piperidin-1-yl]-propylamine.**

To a solution of 4-(2-methoxy-5-methyl)-phenyl-4-phenyl-piperidine (0.6 g, 2.1 mmol) in 30 mL dioxane was added 3-bromo-N-tert-butoxycarbonyl-propylamine (0.6 g, 2.5 mmol) and  $\text{K}_2\text{CO}_3$  (0.6 g, 6.0 mmol) and the resulting suspension was heated to reflux for 10 h. The suspension was allowed to cool, filtered and the solvent was evaporated to obtain yellow residue which was purified by column chromatography ( $R_f = 0.4$ , 3:1 EtOAc/MeOH) to obtain 3-[4-(2-methoxy-5-methyl)phenyl-4-phenyl-piperidin-1-yl]-N-tert-butoxycarbonyl-propylamine as a yellow oil (0.35 g). It was dissolved in 15 mL of  $\text{CH}_2\text{Cl}_2$  and 3.0 mL of trifluoroacetic acid was added with stirring at room temperature under argon atmosphere for 1 h. The solvent was evaporated in vacuo and the residue was basified to pH 10 by adding minimum amount of 1 N KOH solution. The product was extracted with  $\text{CH}_2\text{Cl}_2$  (3 X 25 mL), dried over  $\text{MgSO}_4$ , filtered and the solvent was removed in vacuo to obtain 3-[4-(2-methoxy-5-methyl)phenyl-4-phenyl-piperidin-1-yl]propylamine as a yellow oil (0.25 g, 35% for two steps). It was used in the next step without further purification.

c) (+)-1,2,3,6-Tetrahydro-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1-{N-[4-(2-methoxy-5-methyl)phenyl-4-phenyl-piperidin-1-yl]propyl}-6-(3,4-difluorophenyl) pyrimidine.

5 To a solution of 3-[4-(2-methoxy-5-methyl)phenyl-4-phenyl-piperidin-1-yl]propylamine (0.12 g, 0.36 mmol) in 5.0 mL THF was added (+)1,6-dihydro-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1-(4-nitrophenoxy) carbonyl-6-(3,4-difluorophenyl)pyrimidine (0.12 g, 0.33 mmol) at room temperature and the resulting yellow solution was stirred for 6 h. The solvent was removed in vacuo and the resulting residue was subjected to column chromatography over silica gel (1:1 hexane/EtOAc to EtOAc to 9:1 EtOAc/MeOH) to obtain (+)-1,2,3,6-tetrahydro-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1-{N-[4-(2-methoxy-5-methyl)phenyl-4-phenyl-piperidin-1-yl]propyl}-6-(3,4-difluorophenyl)pyrimidine (0.12 g, 65%) as a yellow oil. It was converted into its HCl salt (pale yellow powder). M.P. 102-105°C.  $[\alpha]_D = +49.4$  (c = 0.65, MeOH) Anal calcd. for  $C_{32}H_{36}N_3O_4F_2Cl \cdot 1.5 CH_2Cl_2$ : C, 55.31; H, 5.40; N, 5.78. Found: C, 55.55; H, 5.06; N, 6.08.

25 **Example 86:**

(+)-1,2,3,6-Tetrahydro-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1-{N-[4-(4-methyl)-phenyl-4-(2-methyl)phenyl piperidin-1-yl]-propyl}-6-(3,4-difluorophenyl) pyrimidine.

30 a) 4-(4-methyl)phenyl-4-(2-methyl)phenylpiperidine hydrochloride.

To a 100 mL round bottom flask equipped with a rubber septum and a stirring bar was added 4-hydroxy-4-(4-methyl)phenyl-piperidine (1.25 g, 6.54 mmol) followed by 20 mL of anhydrous toluene. The resulting solution was stirred at room temperature under argon atmosphere and then  $AlCl_3$  (1.4 g, 10.2 mmol) was added

in one portion. An exotherm was observed. The reaction mixture was stirred for 10 h and then poured carefully over 100 ml of ice-water. The white solid that precipitated out was filtered and washed

5 thoroughly with water followed by diethyl ether to obtain 4-(4-methyl)phenyl-4-(2-methyl)phenylpiperidine hydrochloride (1.95 g, 99%) as a white solid. Mass spectrum: 266 (M+1, 100%). Anal calcd. for  $C_{19}H_{24}NCl \cdot 0.15 CH_2Cl_2$ : C, 73.11; H, 7.79; N, 4.45. Found: C, 73.33; H, 7.82; N, 3.92.

10 **b) 3-[4-(4-methyl)phenyl-4-(2-methyl)phenylpiperidin-1-yl]-propylamine.**

To a solution of 4-(4-methyl)-phenyl-4-(2-methyl)phenyl piperidine hydrochloride (2.6 g, 9.8 mmol) in 100 mL dioxane was added 3-bromo-N-tert-butoxycarbonyl-propylamine (2.57 g, 10.8 mmol) and  $K_2CO_3$  (4.06 g, 29.4 mmol) and the resulting suspension was heated to reflux for 10 h. The suspension was allowed to cool, filtered and the solvent was

15 evaporated to obtain a yellow residue which was purified by column chromatography over silica gel ( $R_f$  = 0.4, 3:1 EtOAc/MeOH) to give 3-[4-(4-methyl)phenyl-4-(2-methyl)phenylpiperidin-1-yl]-N-tert-butoxycarbonyl-propylamine as a yellow oil (2.30 g).

25 It was dissolved in 60 mL of  $CH_2Cl_2$  and 10.0 mL of trifluoroacetic acid was added with stirring at room temperature under argon atmosphere for 1 h. The solvent was evaporated in vacuo and the residue was basified to pH 10 by adding minimum amount of 1 N KOH solution. The product was extracted with  $CH_2Cl_2$  (3 X 25 mL), dried over  $MgSO_4$ , filtered and the solvent was removed in vacuo to obtain 3-[4-(4-methyl)-phenyl-4-(2-methyl)phenyl piperidin-1-yl]propylamine as a yellow oil (1.39 g, 44% for two steps). It was

35 used in the next step without further purification.

**c) (+)-1,2,3,6-Tetrahydro-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1-[N-[4-(4-methyl)-phenyl-4-(2-**

**methyl)phenylpiperidin-1-yl]-propyl}-6-(3,4-difluorophenyl)pyrimidine.**

To a solution of 3-[4-(4-methyl)phenyl-4-(2-methyl)phenyl-piperidin-1-yl]propylamine (0.10 g, 0.31 mmol) in 10.0 mL THF was added (+)-1,6-Dihydro-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1-(4-nitrophenyloxy)carbonyl-6-(3,4-difluorophenyl)pyrimidine (0.10 g, 0.28 mmol) at room temperature and the resulting yellow solution was stirred for 8 h. The solvent was removed in vacuo and the resulting residue was subjected to column chromatography over silica gel (1:1 hexane/EtOAc to EtOAc to 9:1 EtOAc/MeOH) to obtain (+)-1,2,3,6-Tetrahydro-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1-{N-[3-[4-(4-methyl)phenyl-4-(2-methyl)phenylpiperidin-1-yl]propyl}-6-(3,4-difluorophenyl)pyrimidine (0.11 g, 70%) as a yellow oil. It was converted into its HCl salt (pale yellow powder). M.P. 103-107°C.  $[\alpha]_D = +104.8$  (c = 0.31, MeOH) Anal calcd. for  $C_{38}H_{46}N_4O_5F_2Cl \cdot 0.66 CH_2Cl_2$ : C, 60.44; H, 6.32; N, 6.71. Found: C, 60.44; H, 6.21; N, 7.19.

**Example 87:**

**(+)-1,2,3,6-Tetrahydro-5-methoxycarbonyl-4-methyl-2-oxo-1-{N-[3-(4-(4-methyl)phenyl-4-(2-methyl)phenylpiperidin-1-yl]propyl}-6-(3,4-difluorophenyl)pyrimidine.**

To a solution of 3-[4-(4-methyl)phenyl-4-(2-methyl)phenyl-piperidin-1-yl]propylamine (0.25 g, 0.78 mmol) in 10.0 mL THF was added (+)-1,6-dihydro-5-methoxycarbonyl-4-methyl-2-oxo-1-(4-nitrophenyloxy)carbonyl-6-(3,4-difluorophenyl)pyrimidine (0.22 g, 0.67 mmol) at room temperature and the resulting yellow solution was stirred for 8 h. The solvent was removed in vacuo and the resulting residue was subjected to column



chromatography over silica gel (1:1 hexane/EtOAc to EtOAc to 9:1 EtOAc/MeOH) to obtain (+)-1,2,3,6-Tetrahydro-5-methoxycarbonyl-4-methyl-2-oxo-1-{N-[3-[4-(4-methyl)phenyl-4-(2-methyl)phenylpiperidin-1-yl]-propyl]-6-(3,4-difluorophenyl)pyrimidine (0.19 g, 64%) as a yellow oil. It was converted into its HCl salt (pale yellow powder). M.P. 143-147°C.  $[\alpha]_D = +79.8$  (c = 0.25, MeOH). Anal. calcd. for  $C_{37}H_{44}N_4O_4F_2Cl \cdot 0.50 CH_2Cl_2$ : C, 62.19; H, 6.26; N, 7.73. Found: C, 62.15; H, 5.92; N, 7.21.

**Example 88:**

**1,2,3,6-Tetrahydro-1-{[4-benzamido-piperidin-1-yl]propyl}-carboxamido-4-methyl-6-(3,4-difluorophenyl)-2-oxo-pyrimidine.**

**a) 4-Amino-1-benzylpiperidine.**

To a solution of hydroxylamine hydrochloride (3.67 g, 52.8 mmol) in water (10 mL) and ethyl alcohol (80 mL) was added 1-benzyl piperidone (10.0 g, 52.8 mmol) at room temperature. The reaction mixture was heated to reflux for 4 h and then stirred at room temperature overnight. The resulting white solid was filtered, washed with ether and dried (8.4 g, 80%). It was added in small portions to a suspension of lithium aluminum hydride (2.3 g, 60.0 mmol) in diethyl ether (150 mL) at room temperature and the suspension was heated to reflux for 8 h. The reaction mixture was cooled to 0°C and quenched with successive addition of water (3 mL), 3 N NaOH (3 mL) and water (9 mL). The white suspension was filtered and the filtrate was dried over  $MgSO_4$ . The solvent was removed in vacuo after filtration. 4-Amino-1-benzyl-piperidine was obtained as a colorless oil (6.0 g). It was used in the next step without purification.

**b) 1-Benzyl-4-benzamidopiperidine.**

To a biphasic solution of 4-amino-1-benzylpiperidine (6.0 g, 31.6 mmol),  $K_2CO_3$  (8.71 g, 63.1 mmol) in  $CH_2Cl_2$

(200 mL) and water (100 mL) was added benzoyl chloride (4.86 g, 34.7 mmol) in 20 mL of  $\text{CH}_2\text{Cl}_2$  at  $0^\circ\text{C}$  with stirring. After stirring for 4 h at room temperature, the layers were separated. The organic layer was washed with water, dried over  $\text{MgSO}_4$  and filtered. The solvent was removed in vacuo to obtain 1-benzyl-4-benzamidopiperidine (8.16 g, 87% yield) as a white solid. It was used in the next step without purification.

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10 **c) 4-Benzamido-piperidine.**

To a suspension of 10% palladium on carbon (0.2 g) in 30 mL of ethyl alcohol was added a solution of 1-benzyl-4-benzamido-piperidine (0.5 g, 1.79 mmol) in ethyl alcohol (10 mL). The resulting suspension was hydrogenated at 100 psi at  $50^\circ\text{C}$  for 30 h after which it was filtered through a pad of celite and the solvent was removed in vacuo to obtain 0.34 g (100%) of 4-benzamidopiperidine as a white solid. It was used in the next step without purification.

15  
20 **d) 1,2,3,6-Tetrahydro-1-{[4-benzamido-piperidin-1-yl]propyl}-carboxamido-4-methyl-6-(3,4-difluorophenyl)-2-oxo-pyrimidine.**

To a solution of 1-(3-bromopropylcarbamoyl)-6-(3,4-difluoro-phenyl)-4-methyl-2-oxo-1,6-dihydropyrimidine-5-carboxylic acid methyl ester (0.04 g, 0.10 mmol) and 4-benzamidopiperidine (0.03 g, 0.15 mmol) in 15 mL of anhydrous THF was added triethylamine (2 mL) and the resulting solution was heated to reflux for 10 h. The suspension was cooled, filtered and the solvent was evaporated. The residue was purified by column chromatography on silica gel with EtOAc/MeOH (5:1) as the eluting system. 1,2,3,6-tetrahydro-1-{[4-benzamidopiperidin-1-yl]propyl}carboxamido-4-methyl-6-(3,4-difluorophenyl)-2-oxo-pyrimidine was obtained as a yellow oil (0.02 g, 37% yield). The product was analyzed as its hydrochloride salt. M.P.  $121-125^\circ\text{C}$ .

Anal calcd. for  $C_{29}H_{34}N_5F_2O_5Cl \cdot 0.53 CHCl_3$ : C, 53.03; H, 5.20; N, 10.37. Found: C, 52.90; H, 5.61; N, 9.97.

**Example 89:**

5     **4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-3-[3-(4-phenyl-4-(thiophen-2-yl)piperidin-1-yl)-propylcarbamoyl]-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester.**

**a) 4-Phenyl-4-(thiophen-2-yl)piperidine.**

10     To a solution of 4-hydroxy-4-phenylpiperidine (1.0 g, 5.6 mmol) and thiophene (0.88 ml, 11 mmol) in 20 ml of  $CH_2Cl_2$  was added  $AlCl_3$  (0.75 g, 5.6 mmol) at  $-78^\circ C$  and the resulting reaction mixture was stirred for 1 h. The reaction mixture was basified with sat'd  
15     aqueous  $NaHCO_3$  and extracted with EtOAc. The organic layer was dried over  $Na_2CO_3$  and concentrated *in vacuo* to provide the product as a colorless oil which was subjected to the following reaction without further purification.

20     **b) 3-(4-Phenyl-4-(thiophen-2-yl)piperidin-1-yl)propylamine.**

A solution of 4-phenyl-4-(thiophen-2-yl)piperidine and 3-Boc-aminopropylbromide (1.0 g, 4.4 mmol) with 1 g of  $K_2CO_3$  in 20 ml of dioxane was stirred at reflux  
25     for 12 h. The reaction mixture was diluted with water and extracted with EtOAc. The organic solution was dried over  $Na_2SO_4$  and concentrated *in vacuo* to yield an oil which was subjected to column chromatography over silica gel (EtOAc) to provide  
30     0.43 g (1.1 mmol, 20% for two steps) of 3-(4-phenyl-4-(thiophene-2-yl)piperidin-1-yl)-propylcarbamic acid *tert*-butyl ester as colorless oil. The ester in 5 ml of  $CH_2Cl_2$  was added with 1 ml of  $CF_3CO_2H$  and resulting solution was stirred for 1 h at  $25^\circ C$ . The reaction  
35     mixture was concentrated *in vacuo* to yield oily mixture, which was dissolved in EtOAc and washed with aqueous  $NaHCO_3$ . Concentration of the reaction mixture

provided the desired product as an oil (0.29 g, 0.96 mmol, 88%) which was used in the next step without further purification.

- 5 c) 4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-3-[3-(4-phenyl-4-(thiophen-2-yl)piperidin-1-yl)propylcarbamoyl]-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester.

To a solution of 6-(3,4-difluorophenyl)-4-methoxymethyl-2-oxo-3,6-dihydro-2H-pyrimidine-1,5-dicarboxylic acid 5-methyl ester 1-(4-nitrophenyl)ester (29 mg, 0.06 mmol) in 2 ml of CH<sub>2</sub>Cl<sub>2</sub> was added 3-(4-phenyl-4-thiophen-2-yl-piperidin-1-yl)propylamine (20 mg, 0.07 mmol) and the resulting solution was stirred for 2 h at 25 °C. The reaction mixture was concentrated in vacuo to provide an oil which was subjected to column chromatography over silica gel (5% MeOH/CHCl<sub>3</sub>) to yield 25 mg (64%) of the desired product which was converted to a HCl salt and recrystallized from EtOAc-Et<sub>2</sub>O to afford 22 mg of the product as a white solid: mp 157-159°C; Anal. Calc. For C<sub>33</sub>H<sub>36</sub>F<sub>2</sub>N<sub>4</sub>O<sub>5</sub>S requires C, 58.6; H, 5.33; N, 8.29. Found: C, 57.3; H, 5.45; 7.90.

**Example 90:**

- 25 4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-3-[3-(4-phenyl-4-(furan-2-yl)piperidin-1-yl)propyl]carbamoyl-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester.

- 30 a) 4-Phenyl-4-(furan-2-yl)piperidine.

To a solution of 4-hydroxy-4-phenyl-piperidine (0.3 g, 1.7 mmol) and furan (0.50 ml, 6.8 mmol) in 20 ml of CH<sub>2</sub>Cl<sub>2</sub> was added AlCl<sub>3</sub> (0.50 g, 3.7 mmol) at 25 °C and the resulting reaction mixture was stirred for 1 h. The reaction mixture was basified with sat'd aqueous NaHCO<sub>3</sub> and extracted with EtOAc. The organic layer was dried over Na<sub>2</sub>CO<sub>3</sub> and concentrated in vacuo to provide a colorless oil which was identified as

the desired product by NMR analysis and subjected to the following reaction without further purification.

**b) 3-(4-Phenyl-4-(furan-2-yl)piperidin-1-yl)propylamine.**

- 5 A solution of 4-phenyl-4-furan-2-yl-piperidine and 3-Boc-aminopropylbromide (0.30 g, 1.3 mmol) with 0.5 g of  $K_2CO_3$  in 20 ml of dioxane was stirred at reflux for 12 h. The reaction mixture was diluted with water and extracted with EtOAc. The organic solution was
- 10 dried over  $Na_2SO_4$  and concentrated *in vacuo* to yield an oil which was subjected to column chromatography over silica gel (EtOAc) to provide 0.21 g (0.54 mmol, 32% for two steps) of 3-(4-phenyl-4-(furan-2-yl)piperidin-1-yl)propylcarbamic acid tert-butyl
- 15 ester as a colorless oil. The ester in 5 ml of  $CH_2Cl_2$  was added with 1 ml of  $CF_3CO_2H$  and resulting solution was stirred for 1 h at 25 °C. The reaction mixture was concentrated *in vacuo* to yield oily mixture, which was dissolved in EtOAc and washed with aqueous
- 20  $NaHCO_3$ . Concentration of the reaction mixture provided the desired product as an oil (0.13 g, 0.45 mmol, 84%).

- c) 4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-3-[3-(4-phenyl-4-(furan-2-yl)piperidin-1-yl)propylcarbonyl]-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester.**
- 25

- To a solution of 6-(3,4-difluorophenyl)-4-methoxymethyl-2-oxo-3,6-dihydro-2H-pyrimidine-1,5-dicarboxylic acid 5-methyl ester 1-(4-
- 30 nitrophenyl)ester (20 mg, 0.04 mmol) in 2 ml of  $CH_2Cl_2$  was added 3-(4-phenyl-4-furan-2-yl-piperidin-1-yl)-propylamine (12 mg, 0.04 mmol) and resulting solution was stirred for 2 h at 25 °C. The reaction mixture was concentrated *in vacuo* to provide an oil which was
- 35 subjected to column chromatography over silica gel (5% MeOH/ $CHCl_3$ ) to yield 22 mg (85%) of the desired product, which was converted to HCl salt and

recrystallized from EtOAc-Et<sub>2</sub>O to afford 18 mg of the product as a white solid: mp 153-155 °C; Anal. Calc. For C<sub>33</sub>H<sub>36</sub>F<sub>2</sub>N<sub>4</sub>O<sub>6</sub> requires C, 60.1; H, 5.46; N, 8.49. Found: C, 58.9; H, 5.53; N, 8.45.

5

**Example 91:**

4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-3-{3-[4-phenyl-4-(1-methylpyrrol-2-yl)-piperidin-1-yl]-propylcarbamoyl}-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester.

10

**a) 4-Phenyl-4-(1-methylpyrrol-2-yl)piperidine.**

To a solution of 4-hydroxy-4-phenylpiperidine (0.5 g, 2.8 mmol) and 1-methylpyrrole (0.50 ml, 5.6 mmol) in 20 ml of CH<sub>2</sub>Cl<sub>2</sub> was added AlCl<sub>3</sub> (0.75 g, 5.6 mmol) at 25 °C and the resulting reaction mixture was stirred for 1 h. The reaction mixture was basified with sat'd aqueous NaHCO<sub>3</sub> and extracted with EtOAc. The organic layer was dried over Na<sub>2</sub>CO<sub>3</sub> and concentrated in vacuo to provide the desired product as a colorless oil.

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**b) 3-[4-Phenyl-4-(1-methylpyrrol-2-yl)piperidin-1-yl]-propylamine.**

A solution of 4-phenyl-4-(1-methylpyrrol-2-yl)-piperidine and 3-Boc-aminopropylbromide (1.0 g, 4.5 mmol) with 1.5 g of K<sub>2</sub>CO<sub>3</sub> in 20 ml of dioxane was stirred at reflux for 12 h. The reaction mixture was diluted with water and extracted with EtOAc. Organic solution was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuo to yield an oil which was subjected to column chromatography over silica gel (EtOAc) to provide 0.44 g (1.1 mmol, 20% for two steps) of 3-[4-phenyl-4-(1-methylpyrrol-2-yl)-piperidin-1-yl]-propylcarbamic acid tert-butyl ester as a colorless oil. The ester in 10 ml of CH<sub>2</sub>Cl<sub>2</sub> was added with 1 ml of CF<sub>3</sub>CO<sub>2</sub>H and resulting solution was stirred for 1 h at 25 °C. The reaction mixture was concentrated in vacuo to yield an oily mixture, which was dissolved

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in EtOAc and washed with aqueous  $\text{NaHCO}_3$ .

Concentration of the reaction mixture provided an oil (0.26 g, 0.87 mmol, 79%) which was identified as the desired product.

- 5      c) 4-(3,4-Difluorophenyl)-6-methoxymethyl-2-oxo-3-{3-[4-phenyl-4-(1-methylpyrrol-2-yl)-piperidin-1-yl]propylcarbamoyl}-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester.

To a solution of 6-(3,4-difluorophenyl)-4-methoxymethyl-2-oxo-3,6-dihydro-2H-pyrimidine-1,5-dicarboxylic acid 5-methyl ester 1-(4-nitrophenyl)ester (24 mg, 0.05 mmol) in 2 mL of  $\text{CH}_2\text{Cl}_2$  was added 3-[4-phenyl-4-(1-methylpyrrol-2-yl)-piperidin-1-yl]-propylamine (15 mg, 0.05 mmol) and  
10      resulting solution was stirred for 2 h at 25 °C.  
15      Reaction mixture was concentrated in vacuo to provide an oil which was subjected to column chromatography over silica gel (5% MeOH/ $\text{CHCl}_3$ ) to yield 22 mg (69%) of the desired product, which was converted to HCl  
20      salt and recrystallized from EtOAc- $\text{Et}_2\text{O}$  to afford 16 mg of the product as a white solid: mp 139-142°C.

**Example 92 (Compound 92, Figure 1A): (+)-1,2,3,6-Tetrahydro-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1-{N-[4-methyl-4-phenyl-piperidin-1-yl]propyl}carboxamido-6-(3,4-difluorophenyl) pyrimidine**  
25

**a. 1-Benzyl-4-methyl-4-piperidinol**

To a solution of 1-benzyl-4-piperidone (5.6 mL, 30.0 mmol) in 50 mL THF was added a solution of methyllithium in THF (24.0 mL, 36 mmol) dropwise at 0°C over 15 min. The reaction mixture was allowed to warm to room temperature over 3 h and then quenched with 30 mL of sat.  $\text{NH}_4\text{Cl}$  solution. The organic layer was  
30      extracted with diethyl ether (2 X 100 mL) and the combined organic layer was washed with brine (100 mL).  
35      The organic layer was separated, dried over  $\text{Na}_2\text{SO}_4$ ,

filtered and the solvent was removed in vacuo to obtain yellow gum. It was purified by column chromatography over silica gel with 9:1 EtOAc-MeOH as the eluting system to obtain 1-benzyl-4-methyl-4-piperidinol as a yellow thick oil (3.6 g, 59% yield).

**b. 1-Benzyl-4-methyl-4-phenyl piperidine**

To a solution of 1-benzyl-4-methyl-4-piperidinol (3.6 g, 17.5 mmol) in 75 mL of benzene was added  $\text{AlCl}_3$  (11.7 g, 87.7 mmol) in one portion at room temperature. After stirring at room temperature for 30 min, the reaction mixture was heated to reflux for 8 h. The red colored solution was allowed to cool and then poured over 100 g of ice-water. It was extracted with EtOAc (2 X 100 mL) and the organic layer was washed with solution of Rochelle's salt. The organic layer was separated, dried over  $\text{Na}_2\text{SO}_4$ , filtered and the solvent was removed in vacuo to obtain 1-benzyl-4-methyl-4-phenyl piperidine as a red oil (4.5 g, 97% yield). It was used in the next step without further purification.

**c. 4-Methyl-4-phenyl piperidine**

To a cooled suspension of 10% Pd-C (0.5 g) in 10 mL methanol was added a solution of 1-benzyl-4-methyl-4-phenyl piperidine (4.5 g, 17.0 mmol) in 40 mL of methanol and the resulting suspension was hydrogenated in a Parr bomb under 250 psi of hydrogen for two days. The suspension was filtered through a pad of celite and the solvent was removed from the filtrate to obtain 4-methyl-4-phenyl piperidine as a yellow solid (3.3 g, 99% yield).

**d. 3-[4-Methyl-4-phenyl-piperidin-1-yl]propylamine**

To a solution of 4-methyl-4-phenyl piperidine (1.61 g, 9.2 mmol) in 100 mL dioxane was added 3-bromo-N-tert-butoxycarbonyl-propylamine (2.25 g, 9.4 mmol) and  $\text{K}_2\text{CO}_3$  (3.48 g, 25.2 mmol) and the resulting suspension was heated to reflux for 10 h. The suspension was allowed to cool, filtered and the solvent was evaporated to obtain yellow residue which was purified by column



chromatography ( $R_f = 0.4$ , 3:1 EtOAc/MeOH) to obtain 3-[4-methyl-4-phenyl-piperidin-1-yl]-N-tert-butoxycarbonyl-propylamine as a yellow oil (2.85 g). It was dissolved in 35 mL of  $\text{CH}_2\text{Cl}_2$  and 6.0 mL of trifluoroacetic acid was added with stirring at room temperature under argon atmosphere. After 1 h the solvent was evaporated in vacuo and the residue was basified to pH 10 by adding minimum amount of 1 N KOH solution. The product was extracted with  $\text{CH}_2\text{Cl}_2$  (3 X 35 mL), dried over  $\text{MgSO}_4$ , filtered and the solvent was removed in vacuo to obtain 3-[4-methyl-4-phenyl-piperidin-1-yl]propylamine as a viscous yellow oil (1.54 g, 73% for two steps). It was used in the next step without further purification. This step "d" is a representative procedure for putting propylamino tether on any piperidine.

**e. (+)-1,2,3,6-Tetrahydro-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1-{N-[4-methyl-4-phenyl piperidin-1-yl]propyl}carboxamido-6-(3,4-difluorophenyl) pyrimidine**

To a solution of 3-[4-methyl-4-phenyl-piperidin-1-yl]propylamine (0.07 g, 0.31 mmol) in 10.0 mL THF was added (+)-1,6-dihydro-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1-(4-nitrophenoxy)carbonyl-6-(3,4-difluorophenyl) pyrimidine (0.10 g, 0.28 mmol) at room temperature and the resulting yellow solution was stirred for 8 h. The solvent was removed in vacuo and the resulting residue was subjected to column chromatography over silica gel (1:1 hexane/EtOAc to EtOAc to 9:1 EtOAc/MeOH) to obtain (+)-1,2,3,6-tetrahydro-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1-{N-[4-methyl-4-phenyl piperidin-1-yl]propyl}carboxamido-6-(3,4-difluorophenyl) pyrimidine (0.11 g, 78%) as a yellow oil. It was converted into its HCl salt (colorless hygroscopic solid).  $[\alpha]_D = +65.4$  ( $c = 0.26$ , MeOH); Anal calcd. for  $\text{C}_{30}\text{H}_{37}\text{N}_4\text{O}_5\text{F}_2\text{Cl}$ .  $1.0 \text{ CH}_2\text{Cl}_2$ : C, 53.80; H, 5.68; N, 8.10. Found: C, 53.79; H,

6.03; N, 7.83.

**Example 93: (Compound 93, Figure 1A) (+)-1,2,3,6-Tetrahydro-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1-**  
**5 {N-[4-(4-fluoro-2-methyl)-phenyl piperidin-1-**  
**yl]propyl}carboxamido-6-(3,4-difluorophenyl) pyrimidine**

**a. 1-Benzyl-4-(4-fluoro-2-methyl)-phenyl-4-piperidinol**

To a cooled solution of n-BuLi (6.0 mL, 15.0 mmol) in  
20 mL THF was added 2-Bromo-4-fluoro toluene (1.9 mL,  
**10** 15.0 mmol) dropwise at -78°C over 15 min. The reaction  
mixture was allowed to warm to 0°C over 1 h and then  
cooled to -78°C. 1-Benzyl-4-piperidone (1.48 mL, 8.0  
mmol) was added to the white slurry and the reaction  
mixture was warmed to 0°C over 2 h. The reaction was  
**15** then quenched with 10 mL of sat. NH<sub>4</sub>Cl solution. The  
organic layer was extracted with diethyl ether (2 X 50  
mL) and the combined organic layer was washed with  
brine (100 mL). The organic layer was separated, dried  
over Na<sub>2</sub>SO<sub>4</sub>, filtered and the solvent was removed in  
**20** vacuo to obtain yellow oil. It was purified by column  
chromatography over silica gel with 3:2 hexane-EtOAc as  
the eluting system to obtain 1-benzyl-4-(4-fluoro-2-  
methyl)-phenyl-4-piperidinol as a yellow thick oil (1.1  
g, 46% yield).

**25 b. 1-Benzyl-4-(4-fluoro-2-methyl)-phenyl-1,2,3,6-**  
**tetrahydropyridine**

To a solution of 1-benzyl-4-(4-fluoro-2-methyl)-phenyl-  
4-piperidinol (1.1 g, 3.68 mmol) in 100 mL toluene was  
added p-toluenesulfonic acid monohydrate (1.39 g, 7.35  
**30** mmol) and the resulting solution was heated to reflux  
for 8 h. The suspension was cooled and the basified  
with 10% KOH solution and extracted with EtOAc (2 X 50  
mL). The organic layer was washed with brine (30 mL).  
The organic layer was separated, dried over Na<sub>2</sub>SO<sub>4</sub>,  
**35** filtered and the solvent was removed in vacuo to obtain  
1-benzyl-4-(4-fluoro-2-methyl)-phenyl-1,2,3,6-  
tetrahydropyridine as a pale yellow oil (0.9 g, 87%

yield). It was used in the next step without further purification.

**c. 3-[4-(4-Fluoro-2-methyl)-phenyl-piperidin-1-yl]propylamine**

5 To a cooled suspension of 10% Pd-C (0.1 g) in 10 mL methanol was added a solution of 1-benzyl-4-(4-Fluoro-2-methyl)-phenyl-1,2,3,6-tetrahydropyridine (0.9 g, 3.2 mmol) in 20 mL of methanol and the resulting suspension was hydrogenated at room temperature under 1 atm of  
10 hydrogen for 10 h. The suspension was filtered through a pad of celite and the solvent was removed from the filtrate to obtain 4-(4-fluoro-2-methyl)-phenyl-piperidine which was converted into its hydrochloride salt (0.62 g, 99% yield). It was used in the next step without further purification. It was converted into 3-  
15 [4-(4-fluoro-2-methyl)phenyl-piperidin-1-yl]propylamine by the usual procedure as described before. These steps (a,b and c) represent a typical procedure for the synthesis of any 3-[4-aryl-piperidine-1-yl]-  
20 prpylamine side chains.

**d. (+)-1,2,3,6-Tetrahydro-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1-{N-[4-(4-fluoro-2-methyl)-phenyl piperidin-1-yl]propyl}carboxamido-6-(3,4-difluorophenyl) pyrimidine**

25 To a solution of 3-[4-(4-fluoro-2-methyl)phenyl-piperidin-1-yl]propylamine (0.08 g, 0.31 mmol) in 10.0 mL THF was added (+)-1,6-dihydro-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1-(4-nitrophenoxy)carbonyl-6-(3,4-difluorophenyl) pyrimidine (0.10 g, 0.28 mmol) at  
30 room temperature and the resulting yellow solution was stirred for 8 h. The solvent was removed in vacuo and the resulting residue was subjected to column chromatography over silica gel (1:1 hexane/EtOAc to EtOAc to 9:1 EtOAc/MeOH) to obtain (+)-1,2,3,6-  
35 tetrahydro-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1-{N-[4-(4-fluoro-2-methyl)-phenyl piperidin-1-yl]propyl}carboxamido-6-(3,4-difluorophenyl) pyrimidine

(0.11 g, 61%) as a yellow oil. It was converted into its HCl salt (pale yellow powder). M.P. = 122-126 °C;  $[\alpha]_D = + 65.4$  (c = 0.26, MeOH); Anal calcd. for  $C_{30}H_{38}N_4O_5F_3Cl \cdot 0.14 CH_2Cl_2$ : C, 56.65; H, 6.04; N, 8.87. Found: C, 56.62; H, 6.17; N, 8.85.

**Example 94 (Compound 94, Figure 1A):** (+)-1,2,3,6-Tetrahydro-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1-{N-[4-(3,4-difluoro)-phenyl piperidin-1-yl]propyl}carboxamido-6-(3,4-difluorophenyl) pyrimidine

To a solution of 3-[4-(3,4-difluoro)phenyl-piperidin-1-yl]propylamine (0.06 g, 0.17 mmol) (synthesized from 1-bromo-3,4-difluorobenzene by the typical procedure as described above in steps a, b), in 10.0 mL THF was added (+)-1,6-dihydro-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1-(4-nitrophenoxy)carbonyl-6-(3,4-difluorophenyl) pyrimidine (0.06 g, 0.16 mmol) at room temperature and the resulting yellow solution was stirred for 8 h. The solvent was removed in vacuo and the resulting residue was subjected to column chromatography over silica gel (1:1 hexane/EtOAc to EtOAc to 9:1 EtOAc/MeOH) to obtain (+)-1,2,3,6-tetrahydro-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1-{N-[4-(3,4-difluoro)-phenyl piperidin-1-yl]propyl}carboxamido-6-(3,4-difluorophenyl) pyrimidine (0.08 g, 85%) as a yellow oil. It was converted into its HCl salt (pale yellow powder). M.P. = 107-111°C;  $[\alpha]_D = + 126.5$  (c = 0.36, MeOH); Anal calcd. for  $C_{29}H_{35}N_4O_5F_4Cl \cdot 0.18 CH_2Cl_2$ : C, 54.22; H, 5.51; N, 8.67. Found: C, 54.23; H, 5.72; N, 8.19.

**Example 95 (Compound 95, Figure 1B):** (+)-1,2,3,6-Tetrahydro-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1-{N-[4-(3,4,5-trifluoro)-phenyl piperidin-1-yl]propyl}carboxamido-6-(3,4-difluorophenyl) pyrimidine

To a solution of 3-[4-(3,4-difluoro)phenyl-piperidin-1-yl]propylamine (0.02 g, 0.06 mmol) (synthesized from 1-

bromo-3,4,5-difluorobenzene by the typical procedure as described before), in 5.0 mL CH<sub>2</sub>Cl<sub>2</sub> was added (+)-1,6-dihydro-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1-(4-nitrophenoxy)carbonyl-6-(3,4-difluorophenyl)pyrimidine (0.02 g, 0.05 mmol) at room temperature and the resulting yellow solution was stirred for 1 h. The solution was subjected to column chromatography over silica gel (1:1 hexane/EtOAc to EtOAc to 9:1 EtOAc/MeOH) to obtain (+)-1,2,3,6-tetrahydro-5-methoxycarbonyl-4-methoxymethyl-2-oxo-1-{N-[4-(3,4,5-trifluoro)-phenyl piperidin-1-yl]propyl}carboxamido-6-(3,4-difluorophenyl) pyrimidine (0.02 g, 65%) as a yellow oil. It was converted into its HCl salt (pale yellow hygroscopic solid).  $[\alpha]_D = +123.0$  (c = 0.15, MeOH); Anal calcd. for C<sub>29</sub>H<sub>35</sub>N<sub>4</sub>O<sub>5</sub>F<sub>4</sub>Cl.1.0 H<sub>2</sub>O: C, 52.37; H, 5.15; N, 8.12. Found: C, 52.36; H, 5.40; N, 7.63.

**Example 96 (Compound 96, Figure 1B)** (+)-1-{3-[4-cyano-4-(2,4-difluorophenyl)piperidin-1-yl]propyl}aminocarbonyl-6-(3,4-difluorophenyl)-1,6-dihydro-4-methoxymethyl-5-methoxycarbonyl-2-pyrimidone.

**4-Cyano-4-(2,4-difluorophenyl)-piperidine-1-carboxylic acid tert-butyl ester.**

To bis(2-chloroethyl)-carbamic acid tert-butyl ester (1.0 g, 3.8 mmol) and 2,4-difluorophenyl acetonitrile (0.581 g, 3.8 mmol) in DMF (35 mL), NaH (95%) (0.258 g, 9.68 mmol) was added in one batch at 0°C. The solution was stirred for 10 minutes at room temperature. When foaming subsided, the solution was heated at 60°C for 24 hours. It was then quenched with water at 0°C and concentrated. The residue was extracted with ethyl acetate (25 mL) and washed three times with water (15 mL). The organic layer was dried over sodium sulfate, filtered and concentrated. Purification by column chromatography (hexane: ethyl acetate 4:1) yielded 0.720 g (62%) of the product as a

syrup.

(3-(4-cyano-4-(2,4-difluorophenyl)piperidin-1-yl)propyl)carbamic acid tert-butyl ester.

5 To 4-Cyano-4-(2,4-difluorophenyl)-piperidine-1-carboxylic acid tert-butyl ester (0.720 g, 2.42 mmol) in 5 ml of dichloromethane, 2 ml of trifluoroacetic acid was added and the solution stirred at room temperature for 1 hour. The solution was concentrated,  
10 neutralized with 10% KOH solution and extracted into 25 ml of dichloromethane. The organic layer was dried over sodium sulfate, filtered and concentrated to give 0.484 g (90%) of 4-(2,4-difluorophenyl)-piperidine-4-carbonitrile which was used as such for the subsequent  
15 step.

To a stirred solution of 4-(2,4-difluorophenyl)-piperidine-4-carbonitrile (0.203 g, 0.914 mmol) in acetone (20 ml), N-(tert-butoxycarbonyl)-3-bromopropylamine (0.239 g, 1.00 mmol) potassium  
20 carbonate (0.505 g, 3.65 mmol) and sodium iodide (0.274 g, 1.82 mmol) were added and the solution refluxed for 24 hours. The reaction mixture was cooled to room temperature, concentrated and partitioned between  
25 chloroform (20 mL) and water (5 mL). The organic layer was dried over sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (ethyl acetate) to yield 0.259 g (75%) of the required product as a colorless oil.

30 (+)-1-{3-[4-cyano-4-(2,4-difluoro)phenylpiperidin-1-yl]propyl}aminocarbonyl-6-(3,4-difluorophenyl)-1,6-dihydro-4-methoxymethyl-5-methoxycarbonyl-2-pyrimidone.  
To 3-(4-cyano-4-(2,4-difluorophenyl)piperidin-1-yl)propyl)-carbamic acid tert-butyl ester (0.259, 0.683  
35 mmol) in 5 ml of dichloromethane, 1 ml of trifluoroacetic acid was added and the solution stirred

at room temperature for 1 hour. The solution was concentrated, neutralized with 10 % KOH solution and extracted into 25 ml of dichloromethane. The organic layer was dried over sodium sulfate, filtered and concentrated to give 0.171 g (90%) of 1-(3-aminopropyl)-4-(2,4-difluorophenyl)-piperidine-4-carbonitrile which was used as such for the subsequent step.

To (+)-6-(3,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-4-methoxymethyl-1-(4-nitro)phenoxy carbonyl-2-pyrimidone (0.05 g, 0.104 mmol) in 10 ml of dry THF, 1-(3-aminopropyl)-4-(2,4-difluorophenyl)piperidine-4-carbonitrile (0.032 g, 0.1152 mmol) was added and the solution was stirred at room temperature for 24 hours. The reaction mixture was concentrated and purified by column chromatography (hexanes: ethyl acetate 1:4) to yield 0.050 g (78%) of the product as a foamy syrup.

To the free base (0.05 g, 0.0809 mmol) in dichloromethane (2 mL), 1N HCl in ether (0.2 mL) was added, and the solution concentrated under reduced pressure. Recrystallization from ether gave 0.05 g (96 %) of the product as a white solid: m.p. 180-192°C;  $[\alpha]_D = 110.6$  (1.95 mg/mL, MeOH). Anal. Calcd. for  $C_{30}H_{32}Cl_1F_4N_5O_5 \cdot 0.60 CH_2Cl_2$ : C, 52.13; H, 4.75; N, 9.93. Found: C, 52.17; H 4.79; N, 10.32.

**Example 97 (Compound 97, Figure 1B):** (+)-1-{3-[4-Cyano-4-(2,4-dichlorophenyl)piperidin-1-yl]propyl}aminocarbonyl-6-(3,4-difluorophenyl)-1,6-dihydro-5-methoxy-carbonyl-4-methoxymethyl-2-pyrimidone.

**4-Cyano-4-(2,4-dichlorophenyl)piperidine-1-carboxylic acid tert-butyl ester.**

- To bis(2-chloroethyl)-carbamic acid tert-butyl ester (1.0 g, 3.8 mmol) and 2,4-dichlorophenyl acetonitrile (0.708 g, 3.8 mmol) in DMF (35 ml), NaH (95 %) (0.258 g, 9.68 mmol) was added in one batch at 0°C.
- 5 The solution was stirred for 10 minutes at room temperature. When foaming subsided, the solution was heated at 60°C for 24 hours. It was then quenched with water at 0°C and concentrated. The residue was
- 10 extracted with ethyl acetate (25 mL) and washed three times with water (15 mL). The organic layer was dried over sodium sulfate, filtered and concentrated. Purification by column chromatography (hexane:ethyl acetate 4:1) yielded 0.620 g (45%) of the product as a syrup.
- 15 **(3-(4-Cyano-4-(2,4-dichlorophenyl)piperidin-1-yl)propyl}carbamic acid tert-butyl ester.**
- To 4-cyano-4-(2,4-dichlorophenyl)piperidine-1-carboxylic acid tert-butyl ester (0.620 g, 1.74 mmol)
- 20 in 5 ml of dichloromethane, 2 ml of trifluoroacetic acid was added and the solution stirred at room temperature for 1 hour. The solution was concentrated, neutralized with 10 % KOH solution and extracted into 25 ml of dichloromethane. The organic layer was dried
- 25 over sodium sulfate, filtered and concentrated to give 0.442 g (99%) of 4-(2,4-dichlorophenyl)piperidine-4-carbonitrile which was used as such for the subsequent step.
- 30 To a stirred solution of 4-(2,4-dichlorophenyl)piperidine-4-carbonitrile (0.736 g, 2.88 mmol) in acetone (20 ml), N-(tert-butoxycarbonyl)-3-bromopropylamine (0.754 g, 3.17 mmol), potassium carbonate (1.594 g, 11.53 mmol) and sodium iodide
- 35 (0.865 g, 5.7 mmol) were added and the solution refluxed for 24 hours. The reaction mixture was cooled to room temperature, concentrated and partitioned



between chloroform (20 mL) and water (5 mL). The organic layer was dried over sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (ethyl acetate) to yield 0.925 g (78 %) of the required product as a colorless oil.

(+)-1-{3-[4-Cyano-4-(2,4-dichloro)phenyl]piperidin-1-yl}propyl}aminocarbonyl-6-(3,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-4-methoxymethyl-2-pyrimidone

To 3-(4-cyano-4-(2,4-dichlorophenyl)piperidin-1-yl)propyl-carbamic acid tert-butyl ester (0.589, 1.42 mmol) in 5 ml of dichloromethane, 1 ml of trifluoroacetic acid was added and the solution stirred at room temperature for 1 hour. The solution was concentrated, neutralized with 10 % KOH solution and extracted into 25 ml of dichloromethane. The organic layer was dried over sodium sulfate, filtered and concentrated to give 0.423 g (93%) of 1-(3-aminopropyl)-4-(2,4-dichlorophenyl)-piperidine-4-carbonitrile which was used as such for the subsequent step.

To (+)-6-(3,4-difluorophenyl)-1,6-dihydro-5-methoxycarbonyl-4-methoxymethyl-1-(4-nitro)phenoxy carbonyl-2-pyrimidone (0.050 g, 0.137 mmol) in 10 ml of dry THF, 1-(3-aminopropyl)-4-(2,4-dichlorophenyl)piperidine-4-carbonitrile (0.047 g, 0.150 mmol) was added and the solution was stirred at room temperature for 24 hours. The reaction mixture was concentrated and purified by column chromatography (hexanes:ethyl acetate 1:4) to yield 0.120 g (94%) of the product as a foamy syrup.

To the free base (0.075 g, 0.1152 mmol) in dichloromethane (2 mL), 1N HCl in ether (0.2 mL) was added, and the solution concentrated under reduced pressure. Recrystallization from ether gave 0.104 g

(88 %) of the product as a white solid: m.p. 194-196°C;  $[\alpha]_D = 108.2$  (1.9 mg/mL, MeOH). Anal. Calcd. for  $C_{30}H_{32}Cl_3F_2N_5O_5 \cdot 0.20 CH_2Cl_2$ : C, 51.53; H, 4.64; N, 9.95. Found: C, 51.86; H 4.75; N, 9.60.

5

**Example 98 (Compound 98, Figure 1C):**  
**(+)-1,2,3,6-Tetrahydro-1-{N-[4-(3-pyridyl)-4-phenylpiperidin-1-yl]propyl}carboxamido-5-methoxycarbonyl-4-methoxymethyl-6-(3,4-difluorophenyl)-2-oxopyrimidine dihydrochloride**

10

**a. 1-Carbethoxy-4-(3-pyridyl)-4-hydroxy-piperidine.** To a flask of THF (200 mL) at -78 °C was added n-butyllithium (24.0 mL, 2.5 M), and the resulting mixture was stirred for 10 min. 3-bromopyridine (5.40 mL, 56.0 mmol) was added to this solution and the resulting mixture was stirred for 30 min. A solution of 1-carbethoxy-4-piperidone (7.24 mL, 48.0 mmol) in THF (20 mL) was cannula to the above anion slowly. The reaction mixture was stirred for 2 hours while warmed to room temperature gradually. Water (100 mL) was added and the mixture was concentrated. Extracted with EtOAc (3 x 100 mL), the organic extract was dried over  $Na_2SO_4$ , filtered and the solvent removed in vacuo. The residue was purified by column chromatography on silica gel with EtOAc and 5% MeOH in EtOAc to give 7.26 g of 1-carbethoxy-4-(3-pyridyl)-4-hydroxyl-piperidine.

15

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**b. 4-(3-Pyridyl)-4-phenyl-piperidine.** To a solution of 1-carbethoxy-4-(3-pyridyl)-4-hydroxyl-piperidine (1.01 g, 4.035 mmol) in benzene (30 mL) at 0 °C was added  $AlCl_3$  (1.0 g, 7.50 mmol) in several portions. The resulting mixture was stirred overnight while warmed to room temperature. Water (20 mL) was added and stirred for 30 min. The mixture was washed with  $CH_2Cl_2$  (100 mL) and the aqueous layer was basified by adding NaOH (20 mL, 20% aq.). Extracted with  $CH_2Cl_2$  (2 x 50 mL), dried ( $K_2CO_3$ ) and the solvent evaporated to afford a residue

30

35

(K<sub>2</sub>CO<sub>3</sub>) and the solvent evaporated to afford a residue as a pale oil (0.83 g, 86%). It was used in the next step without further purification.

5      **c. 1-(3-tert-Butoxycarbonylamino)propyl-4-(3-pyridyl)-4-phenyl-piperidine.** To a solution of 4-(3-pyridyl)-4-phenyl-piperidine (0.83 g, 3.48 mmol) and 3-bromo-N-tert-butoxycarbonylpropylamine (1.244 g, 5.225 mmol) in dioxane (10 mL), was added K<sub>2</sub>CO<sub>3</sub> (4.81 g) and KI (0.1 g). The resulting suspension was heated at 100 °C for 4 hours. The mixture was filtered, concentrated, and purified by chromatography column on silica gel with CHCl<sub>3</sub>/MeOH/NH<sub>3</sub> in MeOH (100:2:0.5) to give the desired product (0.69 g, 50%) as an oil.

15      **d. 1-(3-Aminopropyl)-4-(3-pyridyl)-4-phenyl-piperidine.** A solution of 1-(3-tert-butoxycarbonylamino)propyl-4-(3-pyridyl)-4-phenyl-piperidine (0.69 g, 1.74 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (4 mL) and TFA (4 mL) was stirred for an hour at room temperature. The mixture was concentrated and basified with NaOH (5 mL, 1 N). Extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 20 mL), dried (K<sub>2</sub>CO<sub>3</sub>) and the solvent evaporated to afford a residue as a yellow oil (0.51 g, 99%). It was used in the next step without further purification.

25      **e. (+)-1,2,3,6-Tetrahydro-1-{N-[4-(3-pyridyl)-4-phenyl piperidin-1-yl]propyl}carboxamido-5-methoxycarbonyl-4-methoxymethyl-6-(3,4-difluorophenyl)-2-oxopyrimidine dihydrochloride.** A solution of (+)-5-methoxycarbonyl-4-methoxymethyl-1,2,3,6-tetrahydro-2-oxo-6-(3,4-difluorophenyl)-1-[4-nitrophenoxy]carbonylpyrimidine (0.29 g, 0.61 mmol), 1-(3-aminopropyl)-4-(3-pyridyl)-4-phenyl-piperidine (0.215 g, 0.73 mmol) in THF (5 mL) was stirred at room temperature for 12 hours. Solvent was evaporated and the residue was redissolved in ethyl acetate (100 mL). It was washed with ice-cold 1N NaOH (4 X 50 mL), brine

(2 X 50 mL) and dried over potassium carbonate. Solvent was evaporated at reduced pressure and the residue was purified by flash chromatography on silica gel (dichloromethane:MeOH:2M ammonia in MeOH, 980:10:10 to 940:30:30 ) to give 0.32 g (84%) of very pure product. The hydrochloride salt was prepared by treatment with 1N HCl in ether. M.P. 140-142 °C;  $[\alpha]_D = +120$  (c = 0.25, MeOH); Anal. Calcd. for  $C_{34}H_{39}N_5O_5F_2Cl_2 \cdot 1.15H_2O \cdot 1.15CH_2Cl_2$ : C, 51.17; H, 5.33; N, 8.49. Found: C, 51.05; H; 5.69; N, 9.91.

**Example 99 (Compound 99, Figure 1C):**

( + ) - 1 , 2 , 3 , 6 - T e t r a h y d r o - 1 - { N - [ 4 - ( 3 , 5 - d i m e t h y l p h e n y l ) p i p e r i d i n - 1 - y l ] p r o p y l } c a r b o x a m i d o - 5 - m e t h o x y c a r b o n y l - 4 - m e t h o x y m e t h y l - 6 - ( 3 , 4 - d i f l u o r o p h e n y l ) - 2 - o x o p y r i m i d i n e h y d r o c h l o r i d e

A solution of (+)-5-methoxycarbonyl-4-methoxymethyl-1,2,3,6-tetrahydro-2-oxo-6-(3,4-difluorophenyl)-1-[(4-nitrophenoxy)carbonyl]pyrimidine (0.513 g, 1.074 mmol), 1-(3-aminopropyl)-4-(3,5-dimethylphenyl)-piperidine (0.252 g, 1.023 mmol; prepared from 4-(3,5-dimethylphenyl)piperidine using similar method described above) in THF (5 mL) was stirred at room temperature for 12 hours. Solvent was evaporated and the residue was redissolved in ethyl acetate (100 mL). It was washed with ice-cold 1N NaOH (4 X 50 mL), brine (2 X 50 mL) and dried over potassium carbonate. Solvent was evaporated at reduced pressure and the residue was purified by flash chromatography on silica gel (dichloromethane:MeOH:2M ammonia in MeOH, 980:10:10 to 940:30:30 ) to give 0.578 g (92%) of very pure product. The hydrochloride salt was prepared by treatment with 1N HCl in ether. M.P. 85-88 °C;  $[\alpha]_D = +123$  (c = 0.15, MeOH); Anal. Calcd. for  $C_{31}H_{39}N_4O_5F_2Cl \cdot 0.7CH_2Cl_2$ : C, 55.95; H, 5.98; N, 8.23. Found: C, 55.82; H; 6.07; N, 8.29.

5

As a specific embodiment of an oral composition of a compound of this invention, 100mg of one of the compounds described herein is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size O hard gel capsule.

Pharmacological Profiles of the Compounds in Cloned Human Adrenergic Receptors.

5 Binding affinities were measured for selected compounds of the invention at six cloned human alpha-1 and alpha-2 receptor subtypes, as well as at the L-type calcium channel. The protocols for these experiments are given below.

10 Protocol for the Determination of the Potency of  $\alpha_1$  Antagonists

15 The activity of compounds at the different human receptors was determined in vitro using cultured cell lines that selectively express the receptor of interest. These cell lines were prepared by transfecting the cloned cDNA or cloned genomic DNA or constructs containing both genomic DNA and cDNA encoding the human  $\alpha$ -adrenergic receptors as follows:

20  $\alpha_{1D}$  Human Adrenergic Receptor: The entire coding region of  $\alpha_{1D}$  (1719 bp), including 150 base pairs of 5' untranslated sequence (5' UT) and 300 bp of 3' untranslated sequence (3' UT), was cloned into the BamHI and ClaI sites of the polylinker-modified eukaryotic expression vector pCEXV-3, called EXJ.HR.  
25 The construct involved the ligation of partial overlapping human lymphocyte genomic and hippocampal cDNA clones: 5' sequence were contained on a 1.2 kb SmaI-XhoI genomic fragment (the vector-derived BamHI site was used for subcloning instead of the internal insert-derived SmaI site) and 3' sequences were contained on an 1.3 kb XhoI-ClaI cDNA fragment (the ClaI site was from the vector polylinker). Stable cell lines were obtained by cotransfection with the plasmid  
30  $\alpha_{1A}$ /EXJ (expression vector containing the  $\alpha_{1A}$  receptor gene (old nomenclature)) and the plasmid pGCCos3neo (plasmid containing the aminoglycoside transferase

35

gene) into LM(tk-) cells using calcium phosphate technique. The cells were grown, in a controlled environment (37°C., 5% CO<sub>2</sub>), as monolayers in Dulbecco's modified Eagle's Medium (GIBCO, Grand Island, NY) containing 25mM glucose and supplemented with 10% bovine calf serum, 100 units/ml penicillin g, and 100 µg/ml streptomycin sulfate. Stable clones were then selected for resistance to the antibiotic G-418 (1 mg/ml), and membranes were harvested and assayed for their ability to bind [<sup>3</sup>H]prazosin as described below (see "Radioligand Binding assays").

The cell line expressing the human  $\alpha_{1D}$  receptor used herein was designated L- $\alpha_{1A}$  (old nomenclature) and was deposited with the American Type Culture Collection, 12301 Parklawn Drive, Rockville, Maryland 20852, U.S.A. under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure. The cell line expressing the human  $\alpha_{1D}$  receptor, was accorded ATCC Accession No. CRL 11138, and was deposited on September 25, 1992.

**$\alpha_{1B}$  Human Adrenergic Receptor:** The entire coding region of  $\alpha_{1B}$  (1563 bp), including 200 base pairs and 5' untranslated sequence (5' UT) and 600 bp of 3' untranslated sequence (3' UT), was cloned into the EcoRI site of pCEXV-3 eukaryotic expression vector. The construct involved ligating the full-length containing EcoRI brainstem cDNA fragment from  $\lambda$  ZapII into the expression vector. Stable cell lines were selected as described above. The cell line used herein was designated L- $\alpha_{1B}$  and was deposited with the American Type Culture Collection, 12301 Parklawn Drive, Rockville, Maryland 20852, U.S.A. under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorganisms for the

Purposes of Patent Procedure. The cell line L- $\alpha_{1B}$  was accorded ATCC Accession No. CR 11139, on September 29, 1992.

5      **$\alpha_{1A}$  Human Adrenergic Receptor:** The entire coding region of  $\alpha_{1A}$  (1401 bp), including 400 base pairs of 5' untranslated sequence (5' UT) and 200 bp of 3' untranslated sequence (3' UT), was cloned into the KpnI site of the polylinker-modified pCEXV-3-derived  
10     eukaryotic expression vector, EXJ.RH. The construct involved ligating three partial overlapping fragments: a 5' 0.6kb HincII genomic clone, a central 1.8 EcoRI hippocampal cDNA clone, and a 3' 0.6Kb PstI genomic clone. The hippocampal cDNA fragment overlaps with the  
15     5' and 3' genomic clones so that the HincII and PstI sites at the 5' and 3' ends of the cDNA clone, respectively, were utilized for ligation. This full-length clone was cloned into the KpnI site of the expression vector, using the 5' and 3' KpnI sites of  
20     the fragment, derived from vector (i.e., pBluescript) and 3'-untranslated sequences, respectively. Stable cell lines were selected as described above. The stable cell line expressing the human  $\alpha_{1A}$  receptor used herein was designated L- $\alpha_{1C}$  (old nomenclature) and was  
25     deposited with the American Type Culture Collection, 12301 Parklawn Drive, Rockville, Maryland 20852, U.S.A. under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure.  
30     The cell line expressing the human  $\alpha_{1A}$  receptor was accorded Accession No. CR 11140, on September 25, 1992.

35     **Radioligand Binding Assays:** Transfected cells from culture flasks were scraped into 5ml of 5mM Tris-HCl, 5mM EDTA, pH 7.5, and lysed by sonication. The cell lysates were centrifuged at 1000 rpm for 5 min at 4°C, and the supernatant was centrifuged at 30,000 x g for



20 min at 4°C. The pellet was suspended in 50mM Tris-HCl, 1mM MgCl<sub>2</sub>, and 0.1% ascorbic acid at pH 7.5. Binding of the  $\alpha_1$  antagonist [<sup>3</sup>H]prazosin (0.5 nM, specific activity 76.2 Ci/mmol) to membrane preparations of LM(tk-) cells was done in a final volume of 0.25 ml and incubated at 37°C for 20 min. Nonspecific binding was determined in the presence of 10  $\mu$ M phentolamine. The reaction was stopped by filtration through GF/B filters using a cell harvester. Inhibition experiments, routinely consisting of 7 concentrations of the tested compounds, were analyzed using a non-linear regression curve-fitting computer program to obtain Ki values.

**$\alpha_2$  Human Adrenergic Receptors:** To determine the potency of  $\alpha_1$  antagonists at the  $\alpha_2$  receptors, LM(tk-) cell lines stably transfected with the genes encoding the  $\alpha_{2A}$ ,  $\alpha_{2B}$ , and  $\alpha_{2C}$  receptors were used. The cell line expressing the  $\alpha_{2A}$  receptor is designated L- $\alpha_{2A}$ , and was deposited on November 6, 1992 under ATCC Accession No. CRL 11180. The cell line expressing the  $\alpha_{2B}$  receptor is designated L-NGC- $\alpha_{2B}$ , and was deposited on October 25, 1989 under ATCC Accession No. CRL10275. The cell line expressing the  $\alpha_{2C}$  receptor is designated L- $\alpha_{2C}$ , and was deposited on November 6, 1992 under ATCC Accession No. CRL-11181. All the cell lines were deposited with the American Type Culture Collection, 12301 Parklawn Drive, Rockville, Maryland 20852, U.S.A. under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure. Cell lysates were prepared as described above (see Radioligand Binding Assays), and suspended in 25mM glycylglycine buffer (pH 7.6 at room temperature). Equilibrium competition binding assay were performed using [<sup>3</sup>H]rauwolscine (0.5nM), and nonspecific binding was determined by incubation with 10 $\mu$ M phentolamine. The bound

radioligand was separated by filtration through GF/B filters using a cell harvester.

#### Determination of the Activity of $\alpha_1$ Antagonists at Calcium Channels

The potency of  $\alpha_1$  antagonists at calcium channels may be determined in competition binding assays of [3H]nitrendipine to membrane fragments of rat cardiac muscle, essentially as described by Glossman and Ferry (Methods in Enzymology 109:513-550, 1985). Briefly, the tissue is minced and homogenized in 50mM Tris-HCl (pH 7.4) containing 0.1mM phenylmethylsulfonyl fluoride. The homogenates are centrifuged at 1000 g for 15 minutes, and the resulting supernatant centrifuged at 45,000 g for 15 minutes. The 45,000 g pellet is suspended in buffer and centrifuged a second time. Aliquots of membrane protein are then incubated for 30 minutes at 37°C in the presence of [3H]nitrendipine (1nM), and nonspecific binding determined in the presence of 10 $\mu$ M nifedipine. The bound radioligand is separated by filtration through GF/B filters using a cell harvester.

The compounds described above were assayed using cloned human alpha adrenergic receptors. The preferred compounds were found to be selective  $\alpha_{1A}$  antagonists. The binding affinities of compounds 13-17 are illustrated in the following table.

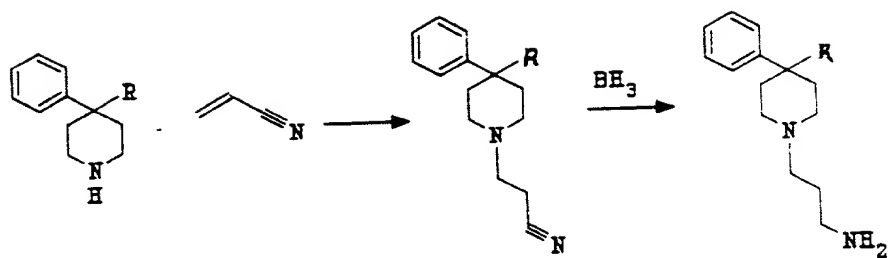
Binding affinities of compounds 13-17 at cloned human  $\alpha 1d$ ,  $\alpha 1b$  and  $\alpha 1a$  receptors.

5

Example	h $\alpha 1d$			h $\alpha 1b$			h $\alpha 1a$		
	pKi	SEM	n	pKi	SEM	n	pKi	SEM	n
13	6.14	0.02	3	6.21	0.09	3	9.74	0.02	3
14	6.46	0.04	3	6.59	0.08	3	9.68	0.05	3
15	6.01	0.03	3	6.33	0.06	3	9.41	0.09	3
16	6.24	0.06	3	6.37	0.06	3	9.54	0.09	3
17	6.17	0.04	4	6.32	0.06	4	8.99	0.12	4

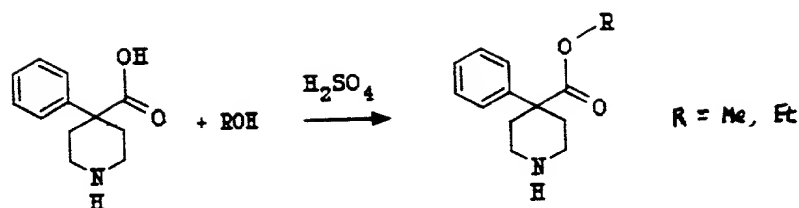
10

h = human

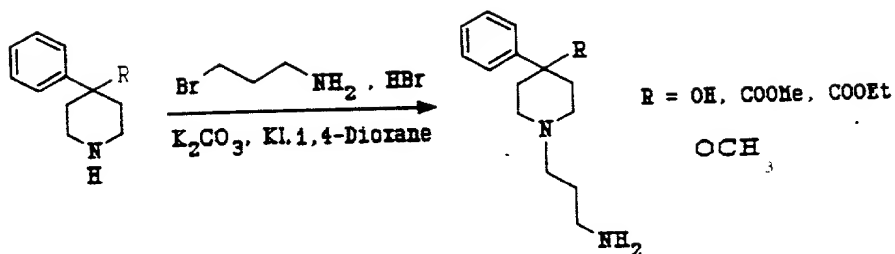


R = H, 4-MeO-Ph

Ph



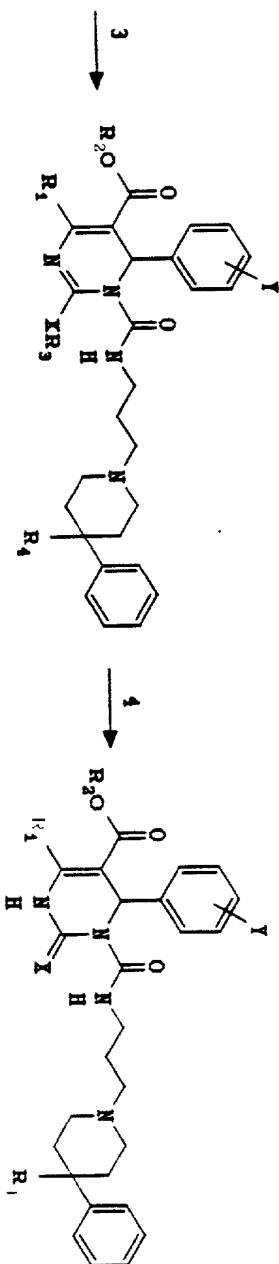
R = Me, Et



R = OH, COOMe, COOEt

OCH<sub>3</sub>

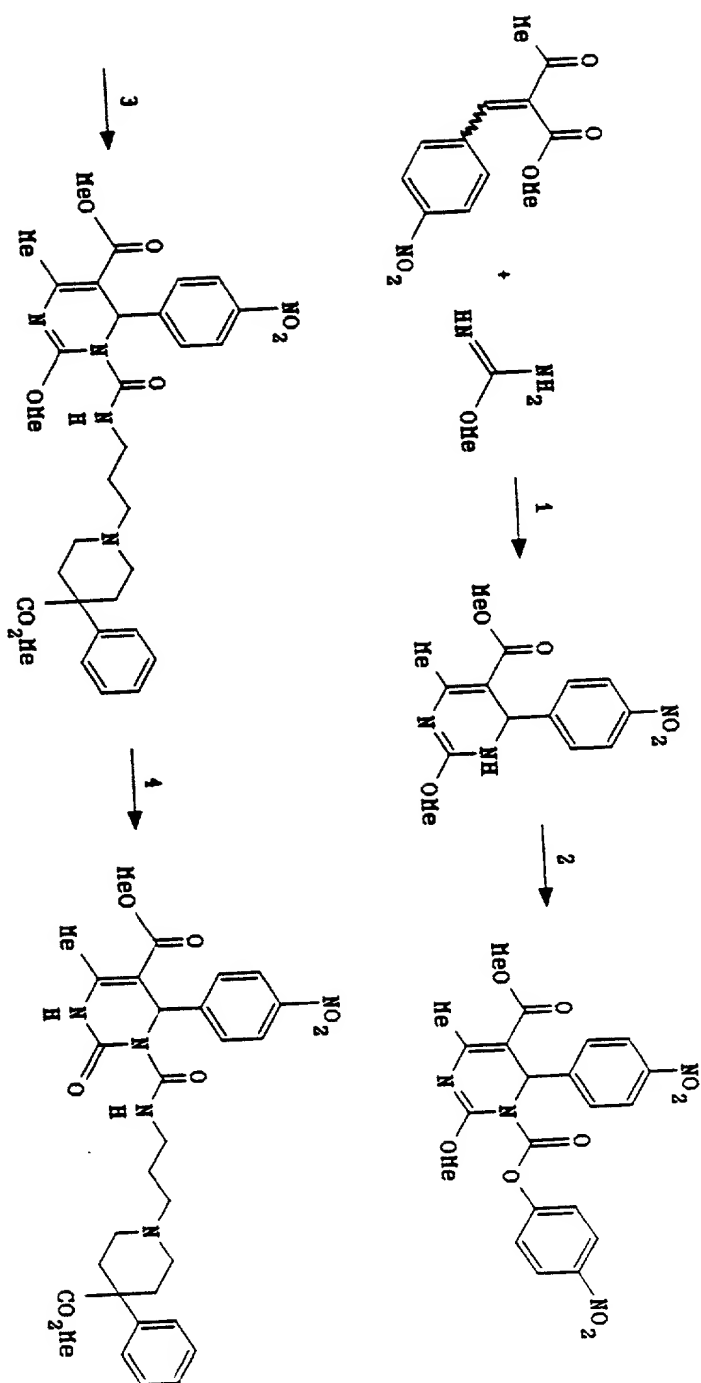
**Scheme 1.** General synthetic schemes for the synthesis of the piperidine sidechains.



- [H+].N=[N+]([O-])CCCC1CCCCC1C2=CC=CC=C2

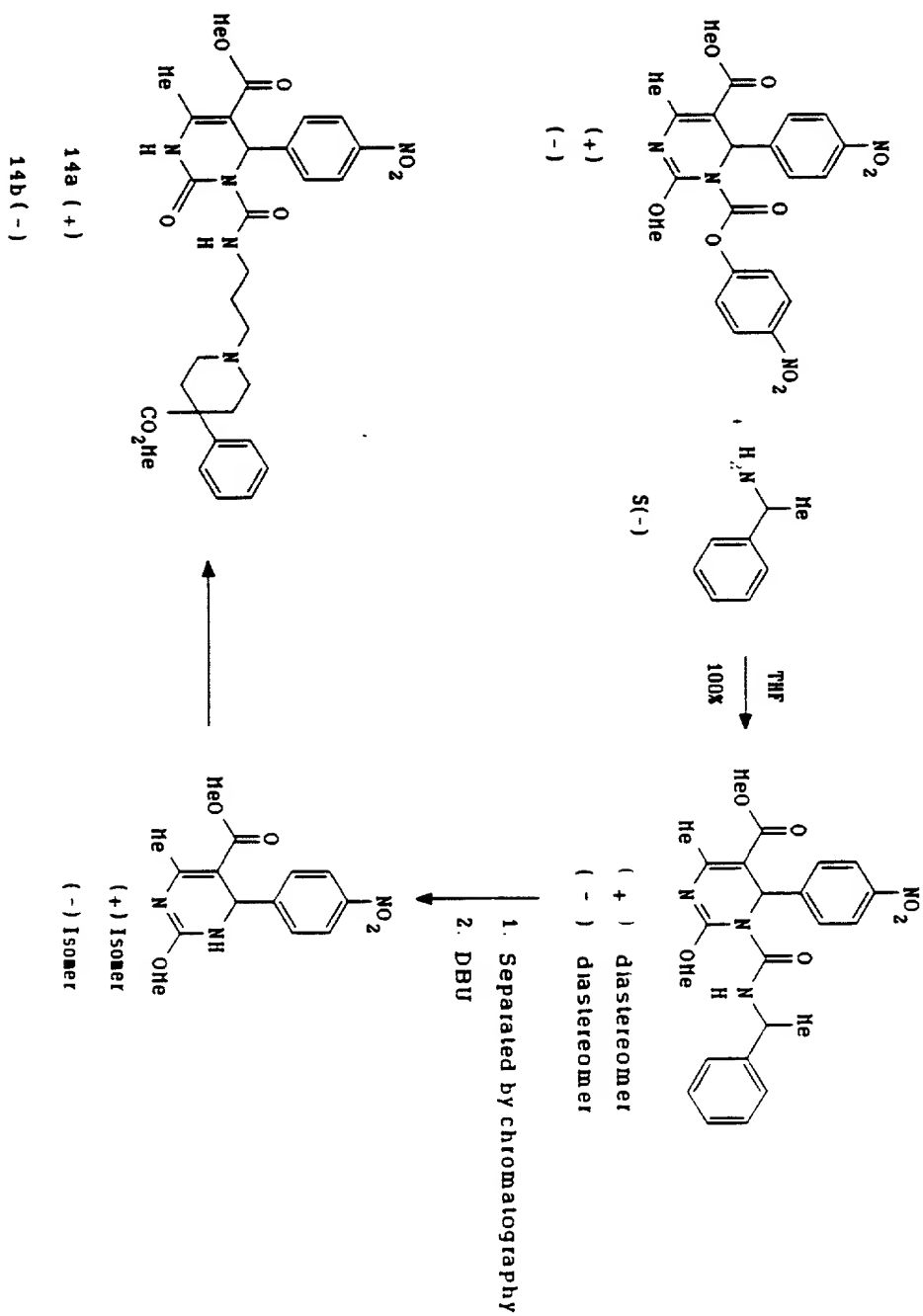
4. HCl/THF or EtSH/TFA.

**Scheme 1 (continued).** General synthetic scheme for examples 1-12.

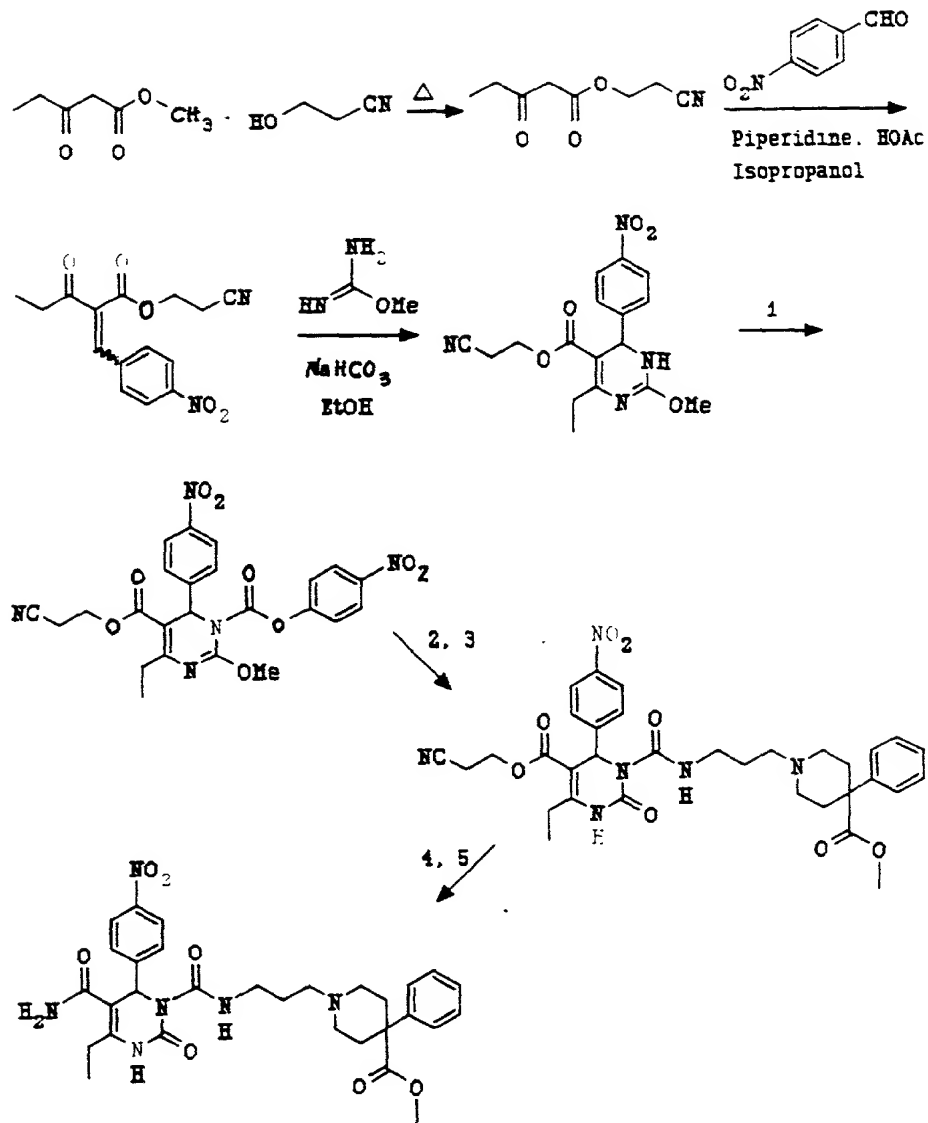


1. NaOAc, DMF.
2. 4-Nitrophenyl chloroformate, NaHCO<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, H<sub>2</sub>O.
3. 3[(4-Methoxycarbonyl-4-phenyl)piperidine-1-yl]propylamine, THF.
4. 6N HCl/THF.

Scheme 2. Synthetic scheme for example 11.



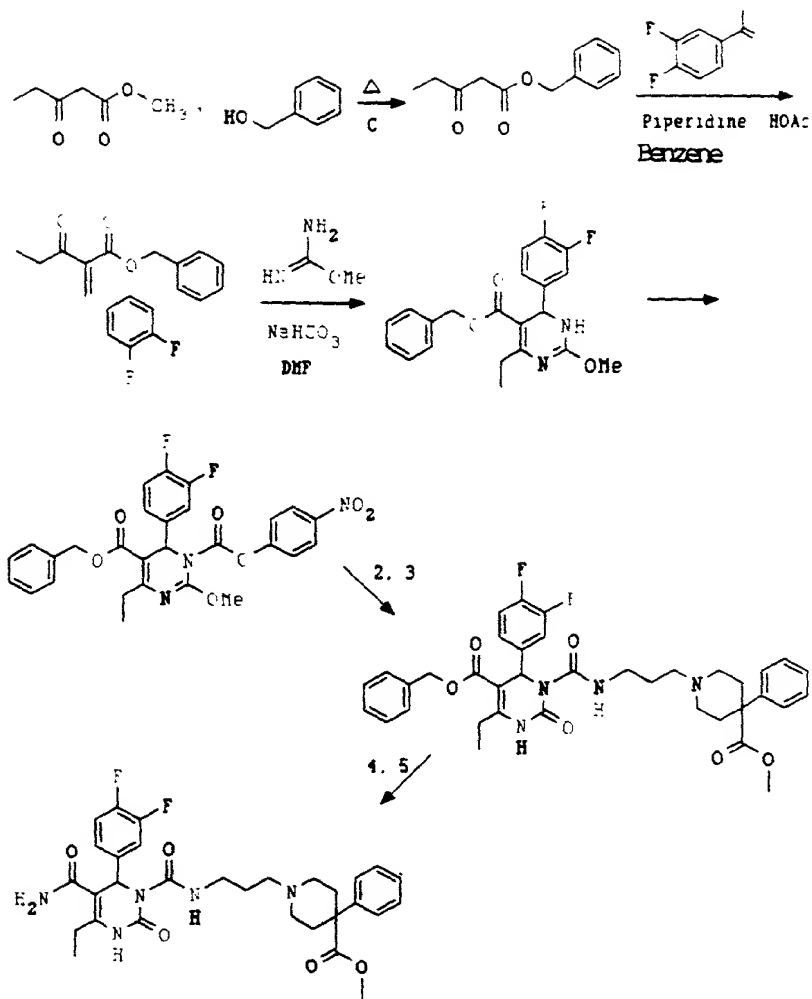
**Scheme 3.** Synthetic scheme for examples 11a and 11b.



1. 4-Nitrophenyl chloroformate,  $\text{NaHCO}_3$ ,  $\text{CH}_2\text{Cl}_2$ ,  $\text{H}_2\text{O}$ .
2. 3-[(4-Methoxycarbonyl-4-phenyl)piperidin-1-yl]propylamine.
3. 6N HCl.
4. NaOH, Acetone.
5. DMAPECD, DMAP,  $\text{NH}_3$ ,  $\text{CH}_2\text{Cl}_2$ .

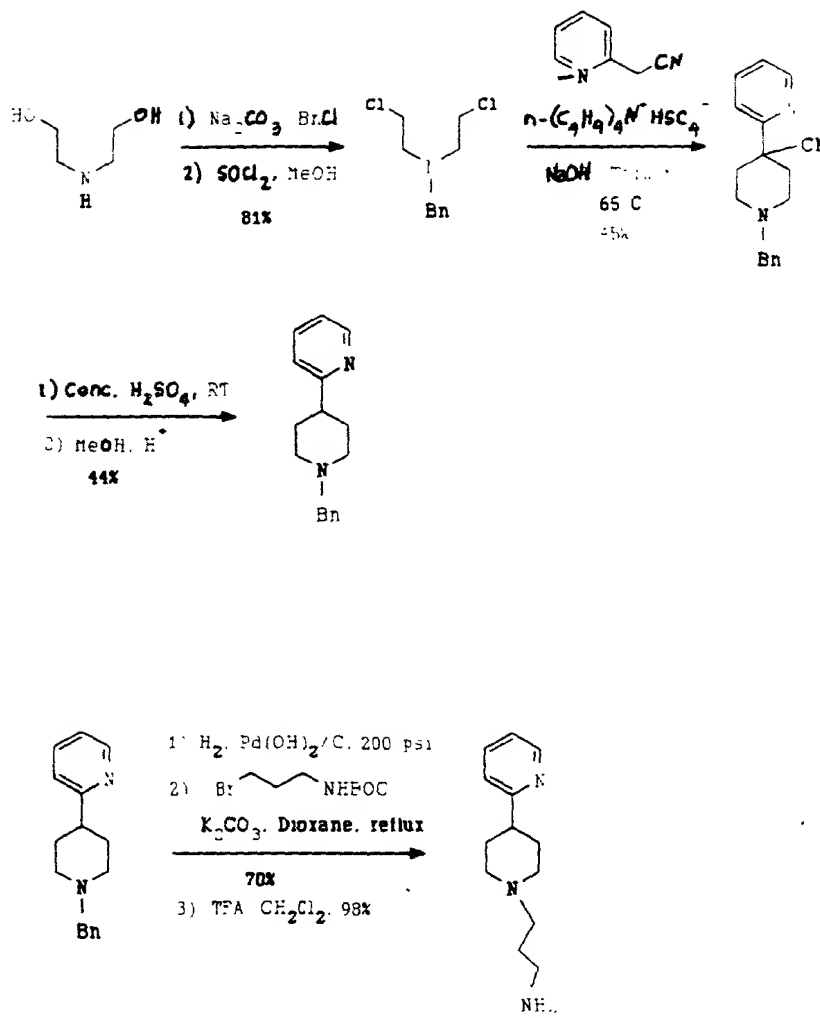
**Scheme 4.** Synthetic scheme for example 13.



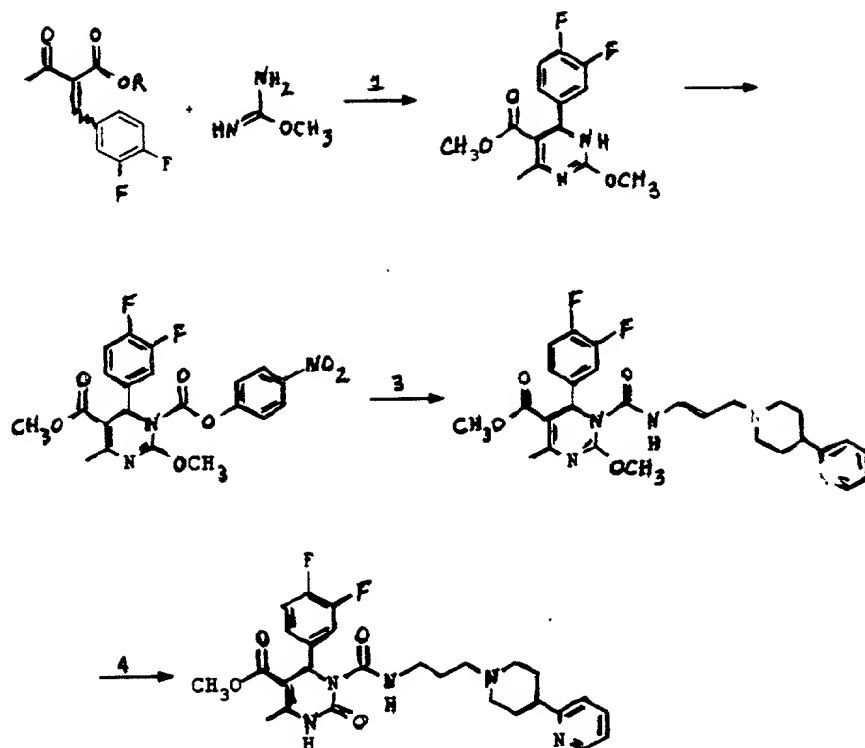


1. 4-Nitrophenyl chloroformate, DMAP, THF
2. 3-[(4-Methoxycarbonyl-4-phenyl)piperidin-1-yl]propylamine.
3. 6N HCl.
4. H<sub>2</sub>, Pd-C, MeOH.
5. DMAPECD, DMAP, NH<sub>4</sub>OH, CH<sub>2</sub>Cl<sub>2</sub>.

**Scheme 5.** Synthetic scheme for example 14.

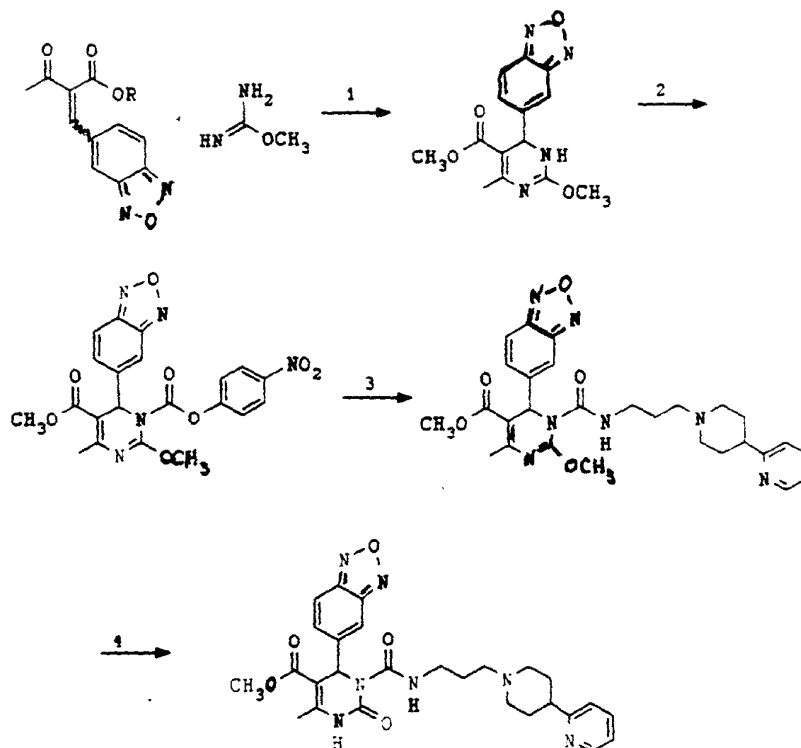


**Scheme 6.** Synthetic scheme for the preparation of 3-[4-(2-Pyridyl)-piperidin-1-yl]propylamine (Example 21 part d).



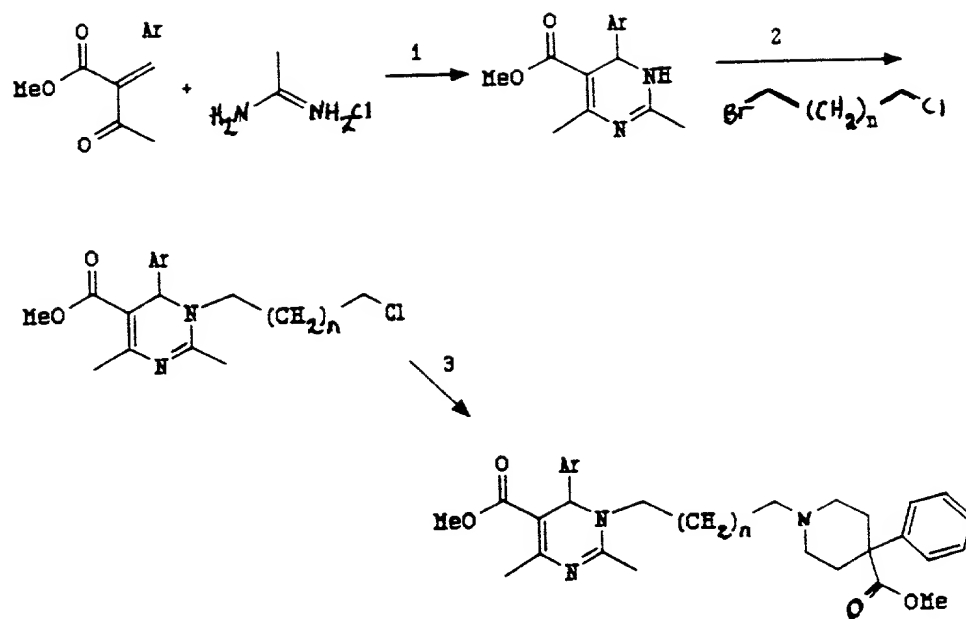
1. NaOAc, DMF.
2. 4-Nitrophenyl chloroformate, NaHCO<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, H<sub>2</sub>O.
3. 3-[(4-(2-Pyridyl)-piperidin-1-yl)propyl]amine, CH<sub>2</sub>Cl<sub>2</sub>.
4. 6N HCl/THF.

**Scheme 7.** Synthetic scheme for example 15.



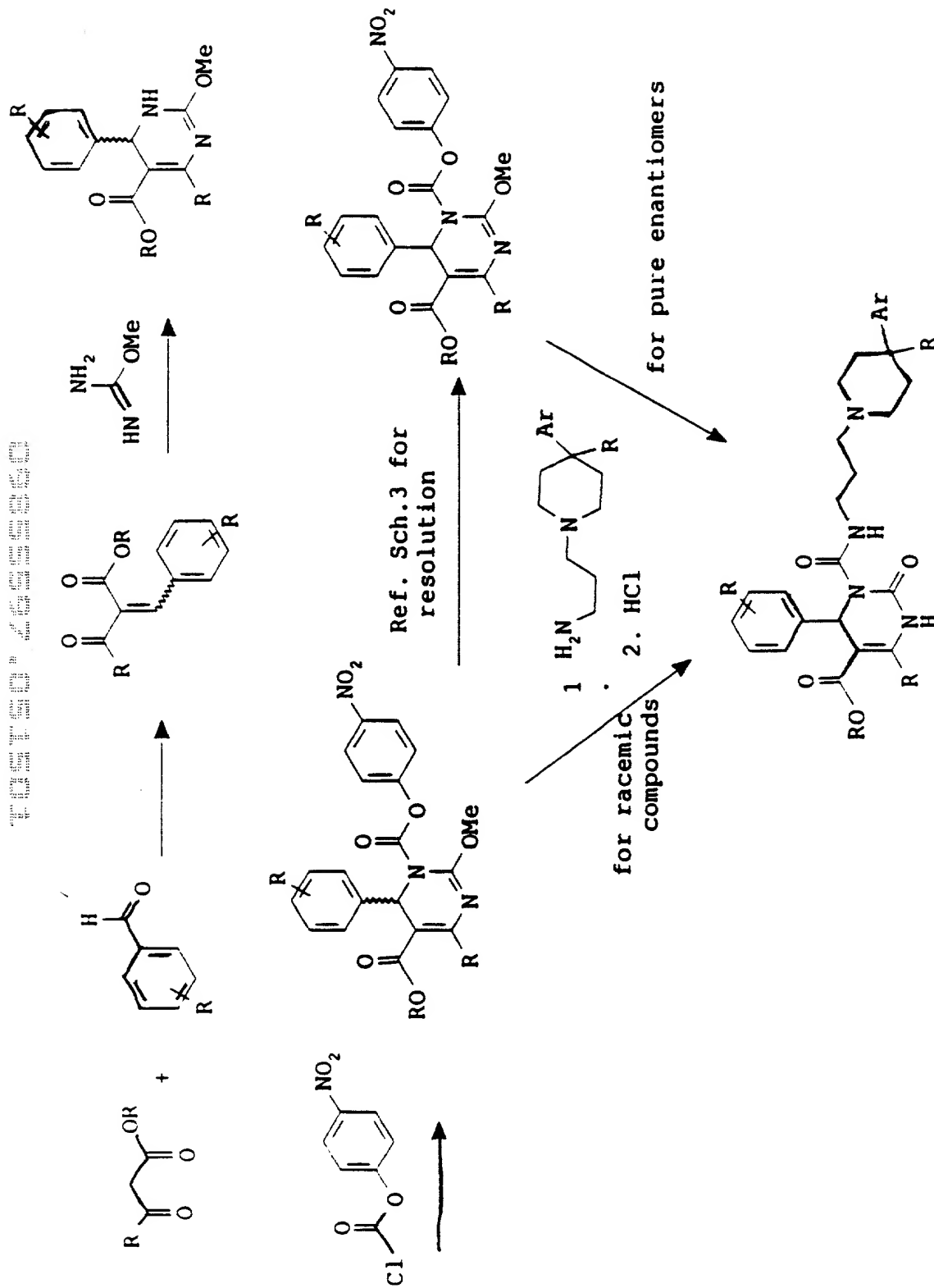
1. NaOAc, DMF.
2. 4-Nitrophenyl chloroformate, NaHCO<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, H<sub>2</sub>O.
3. 3-[(4-(2-Pyridyl)-piperidin-1-yl)propyl]amine, CH<sub>2</sub>Cl<sub>2</sub>.
4. 6N HCl/THF.

**Scheme 8.** Synthetic scheme for example 16.

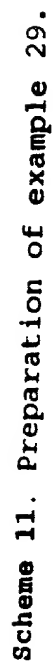


1. (a) *t*-BuOK, DMF, 0°C; (b) TsOH·H<sub>2</sub>O, DMF, 100-120°C.
2. NaH, THF, reflux.
3. 4-Methoxycarbonyl-4-phenylpiperidine, K<sub>2</sub>CO<sub>3</sub>, NaI, 1,4-dioxane, reflux.

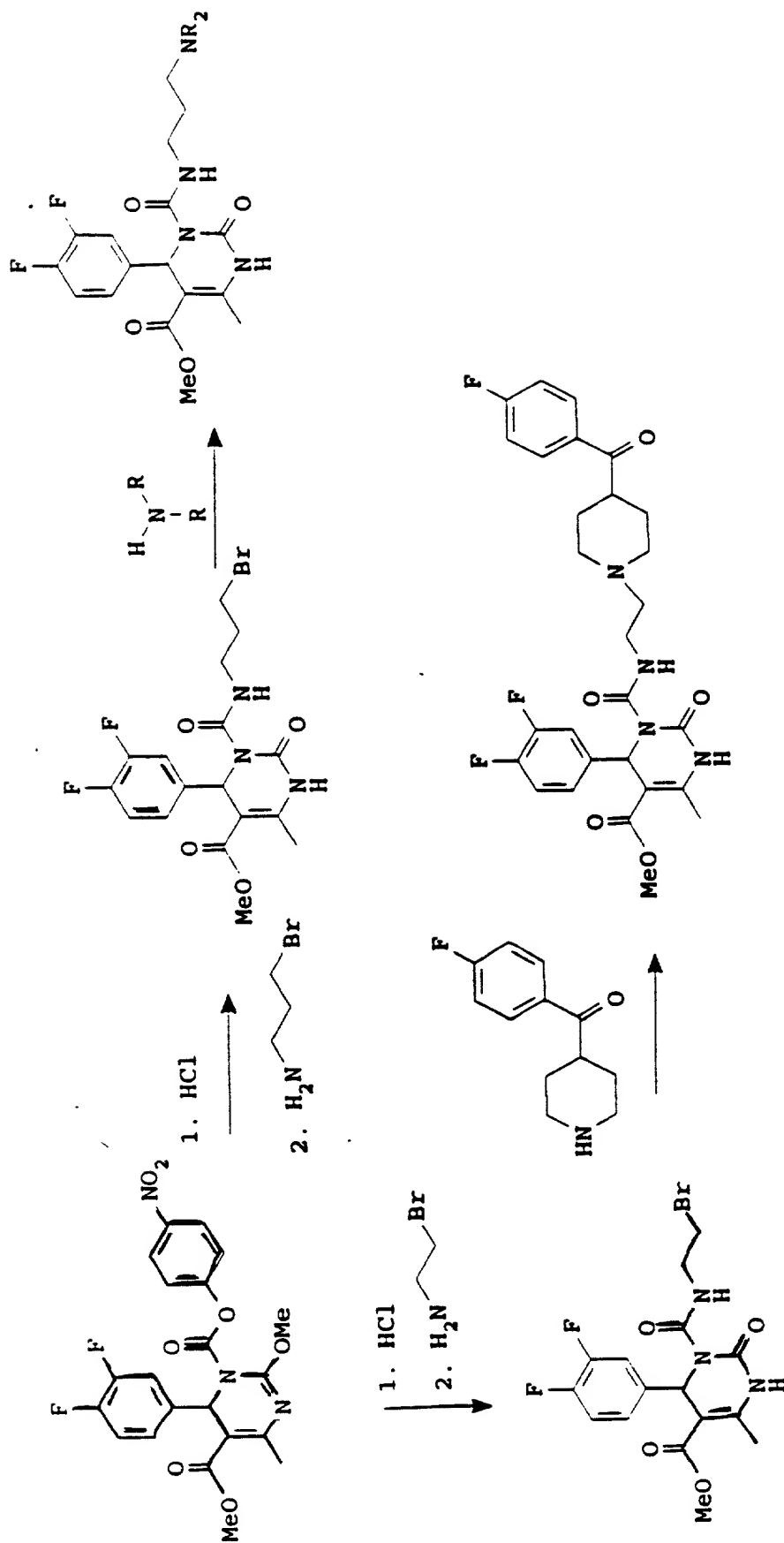
**Scheme 9.** Synthetic scheme for example 17.



Scheme 10. General synthetic scheme for examples 18, 41, 42, 43, 44, and 45.

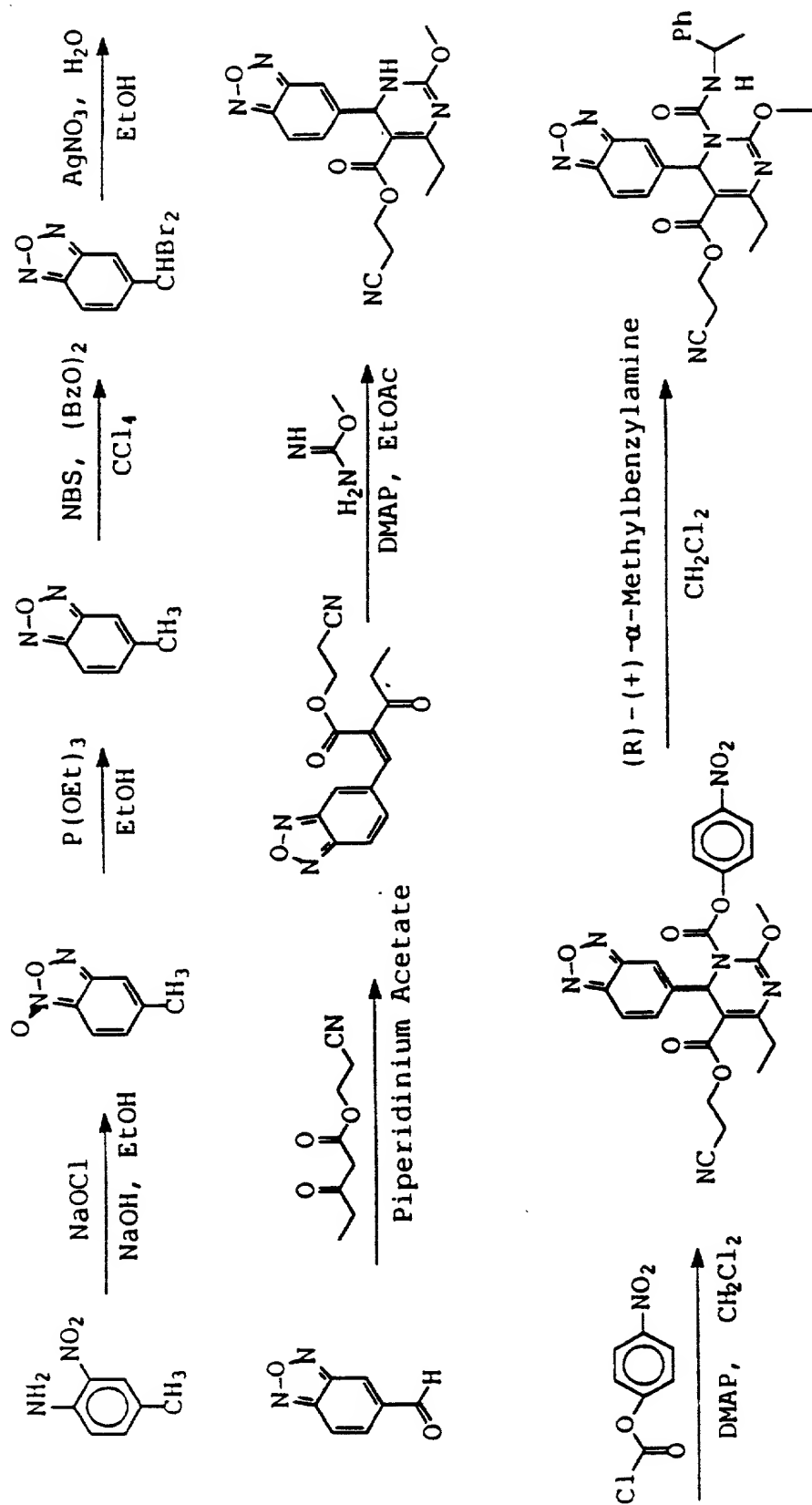


**Scheme 11. Preparation of example 29.**

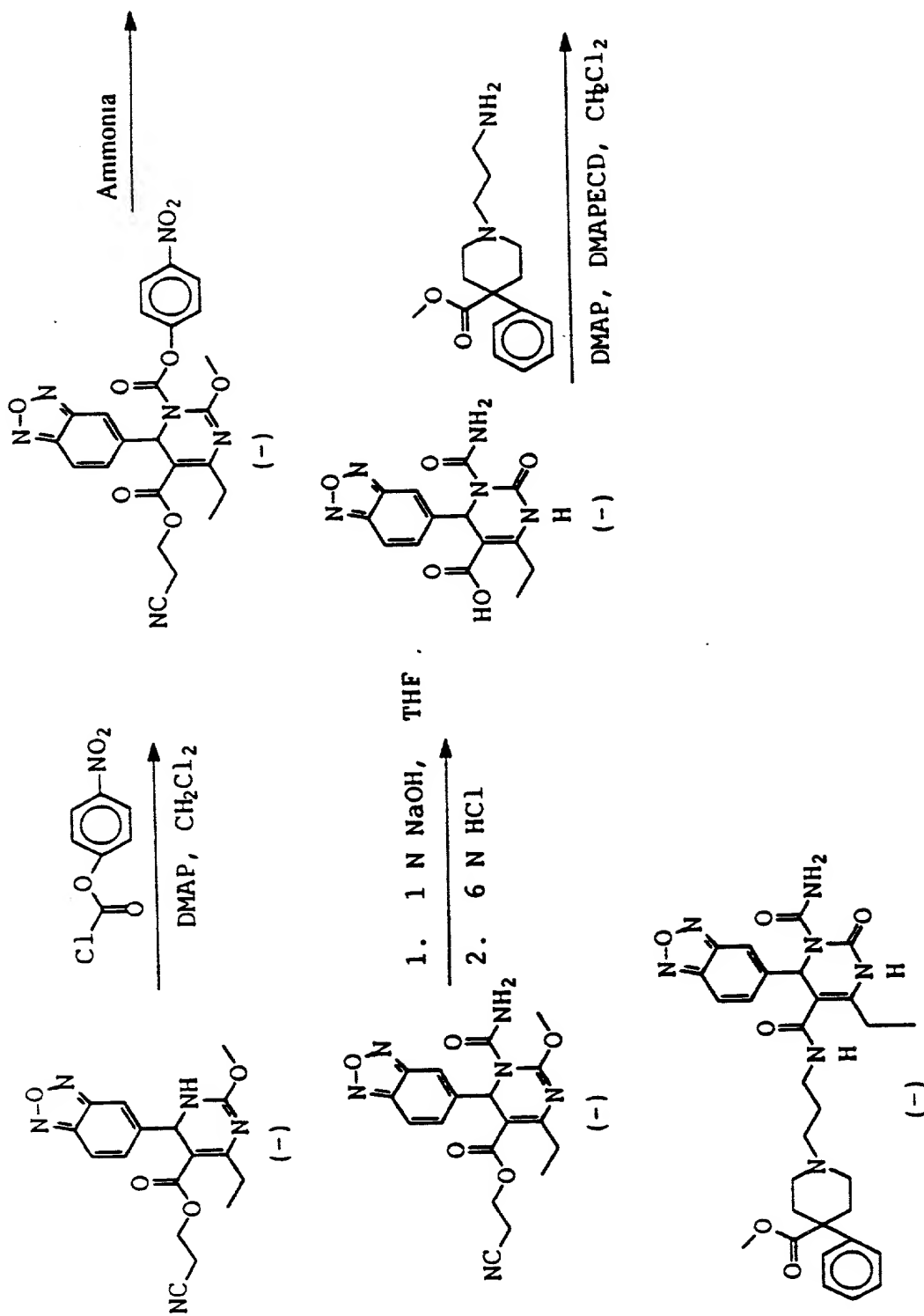


**Scheme 12. General synthetic scheme for examples 30, 31, 35, 37, 39, 40, 47 and 48.**

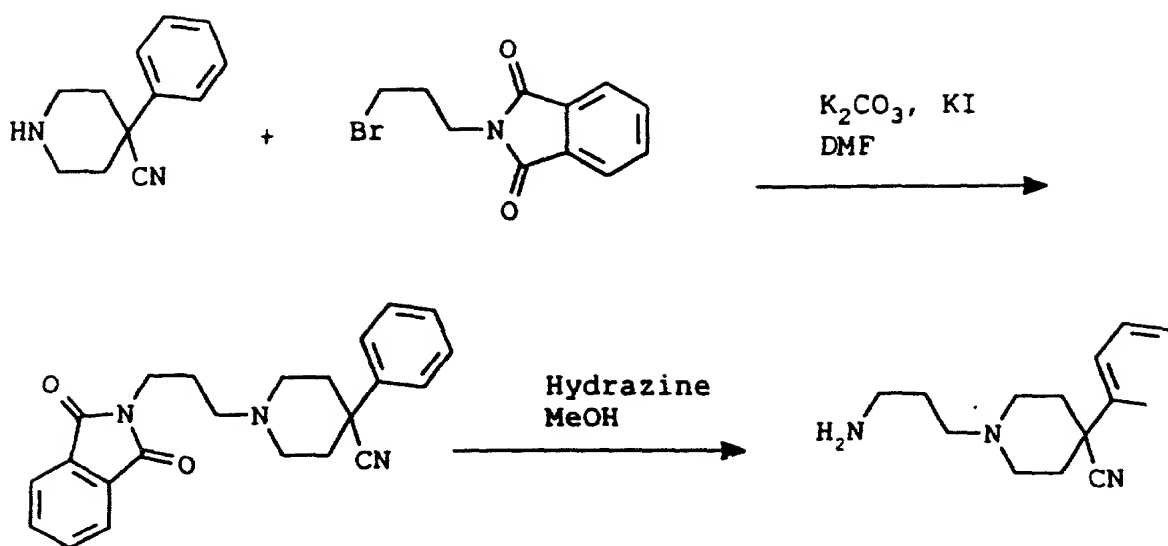




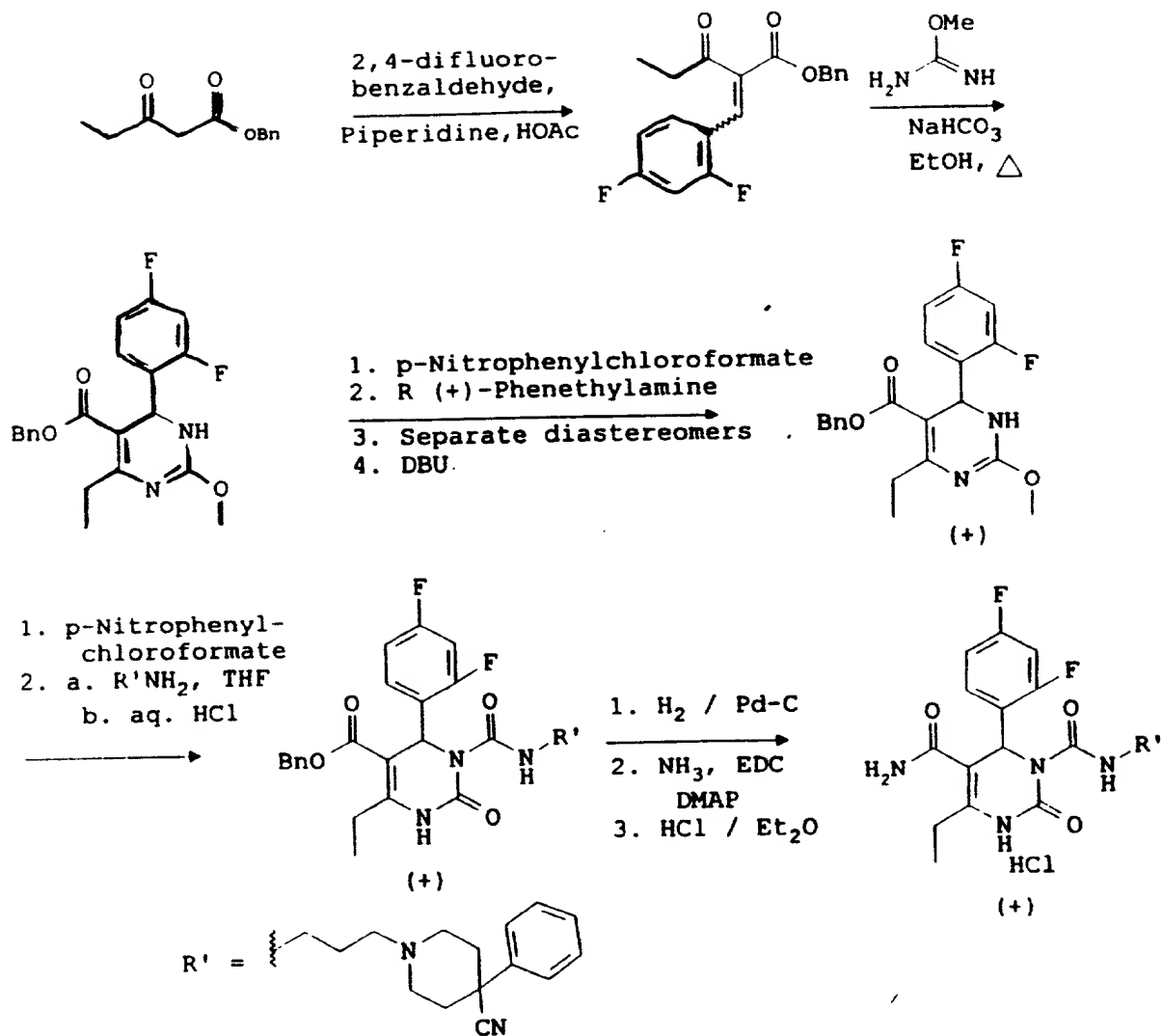
**Scheme 13.** Preparation of example 37 part-1



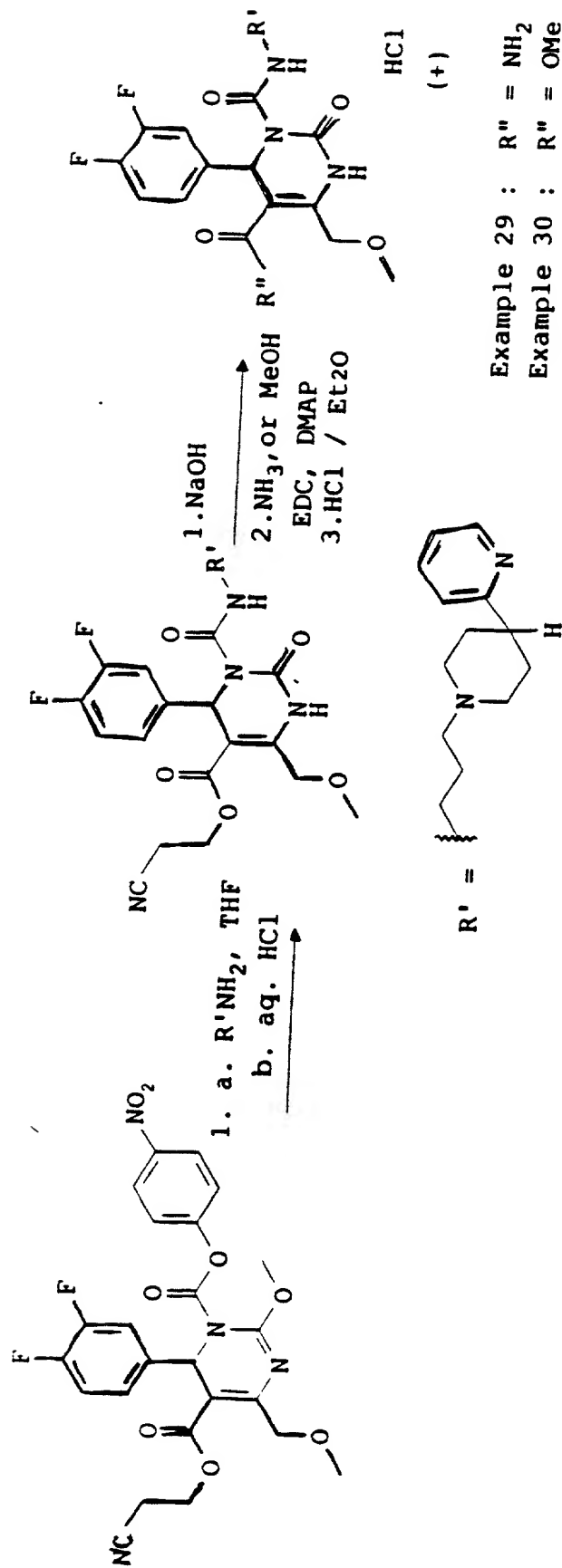
Scheme 13 (continued). Preparation of example 37 part-2



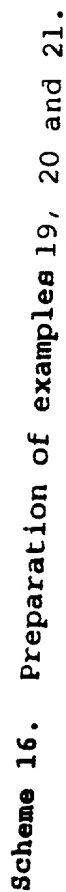
Scheme 14. Preparation of example 22 (part-1)



Scheme 14 (cont.). Preparation of example 22 (part-2)

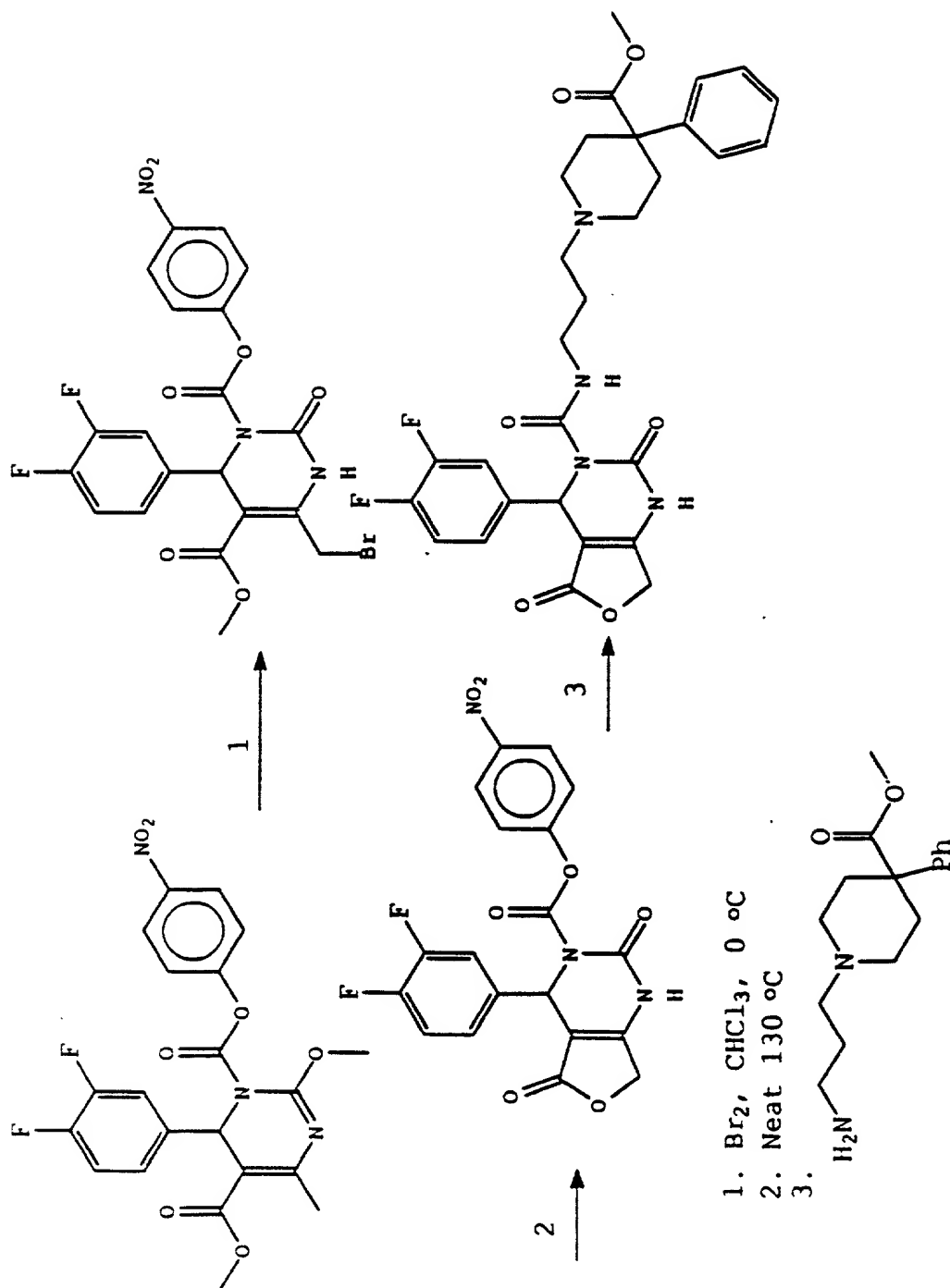


Scheme 15. Preparation of examples 23 and 24



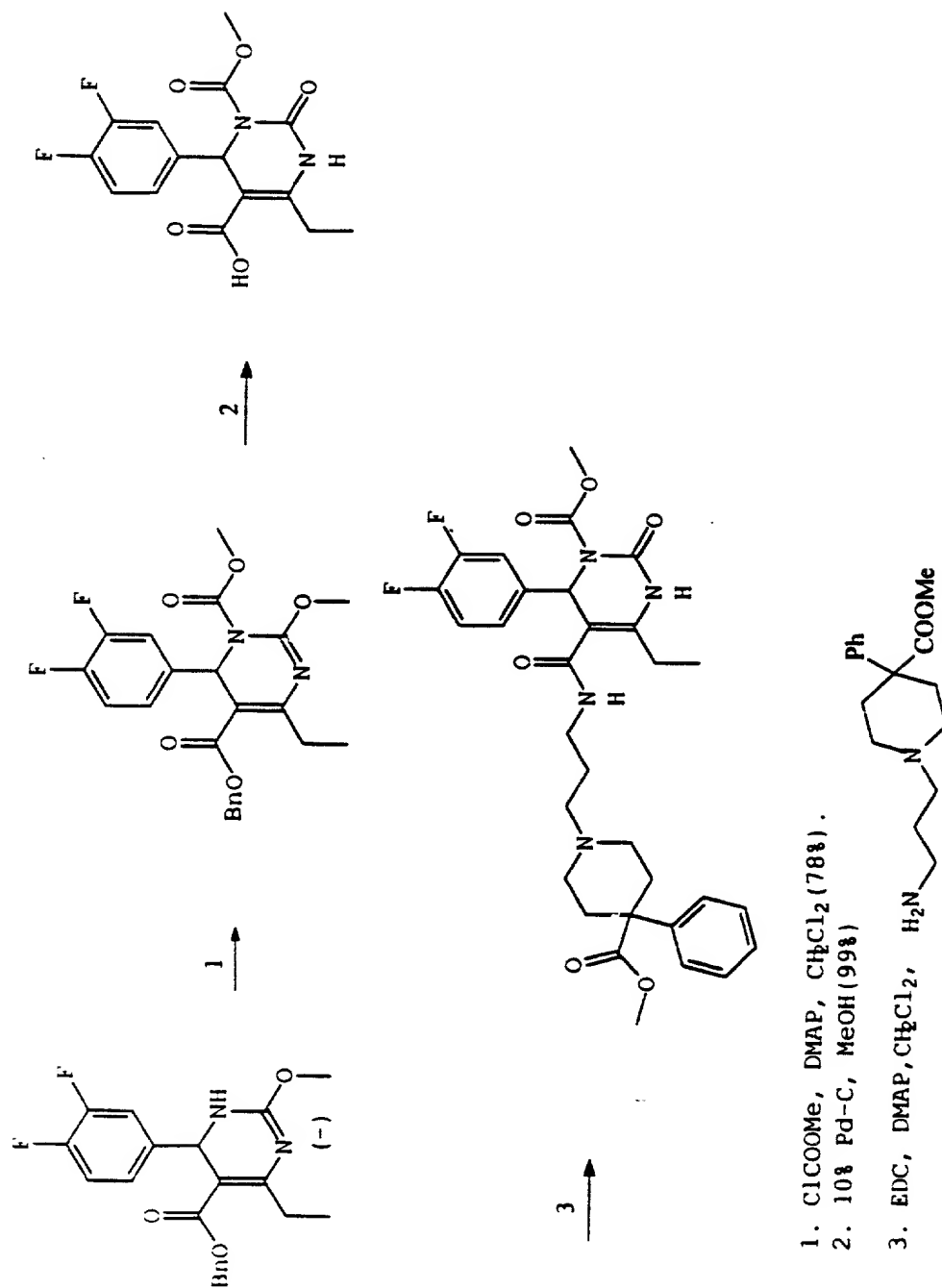


**Scheme 17.** preparation of examples 25, 26, 27 and 28.

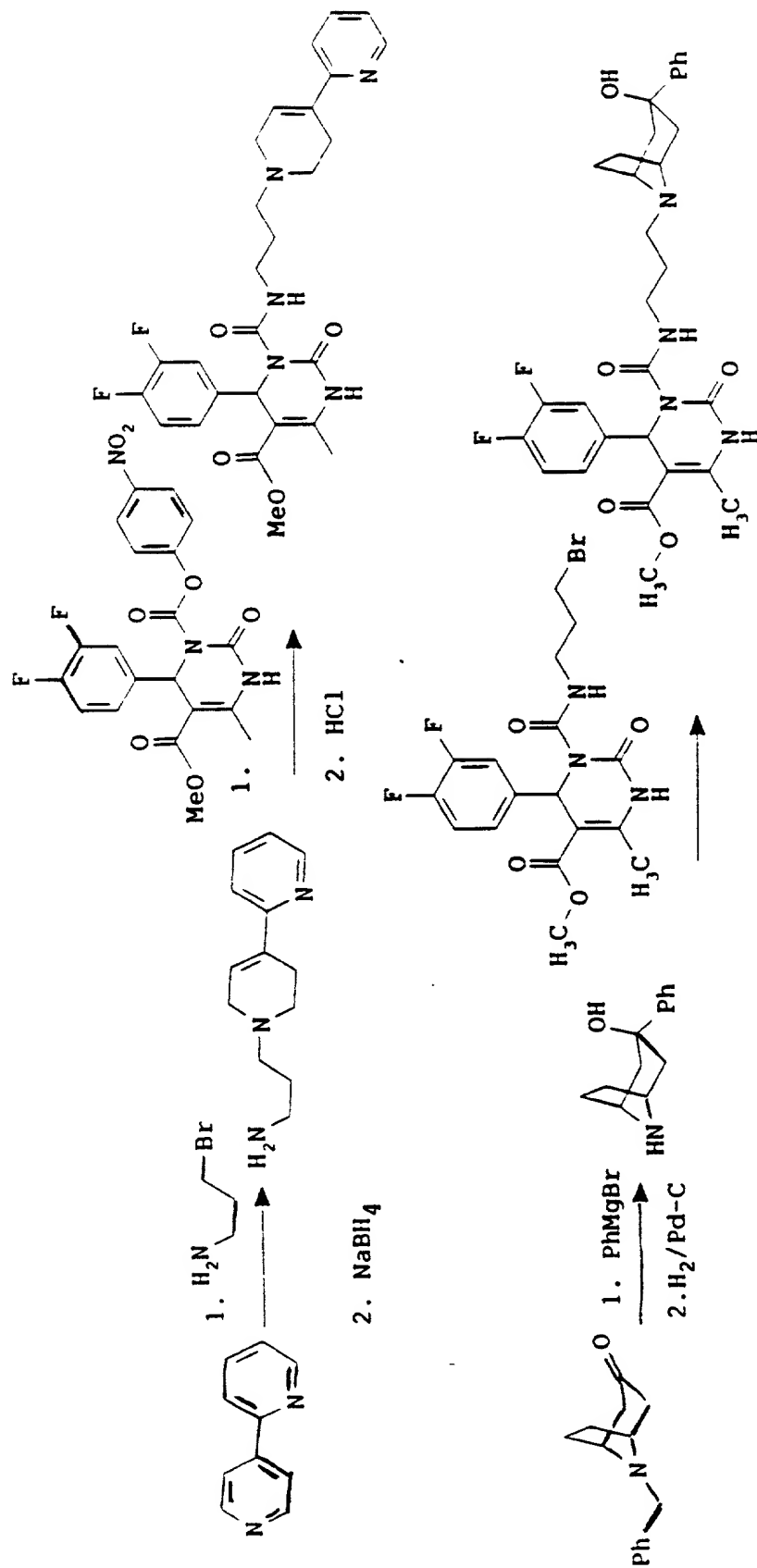


Scheme 18. Preparation of examples 33 and 34.

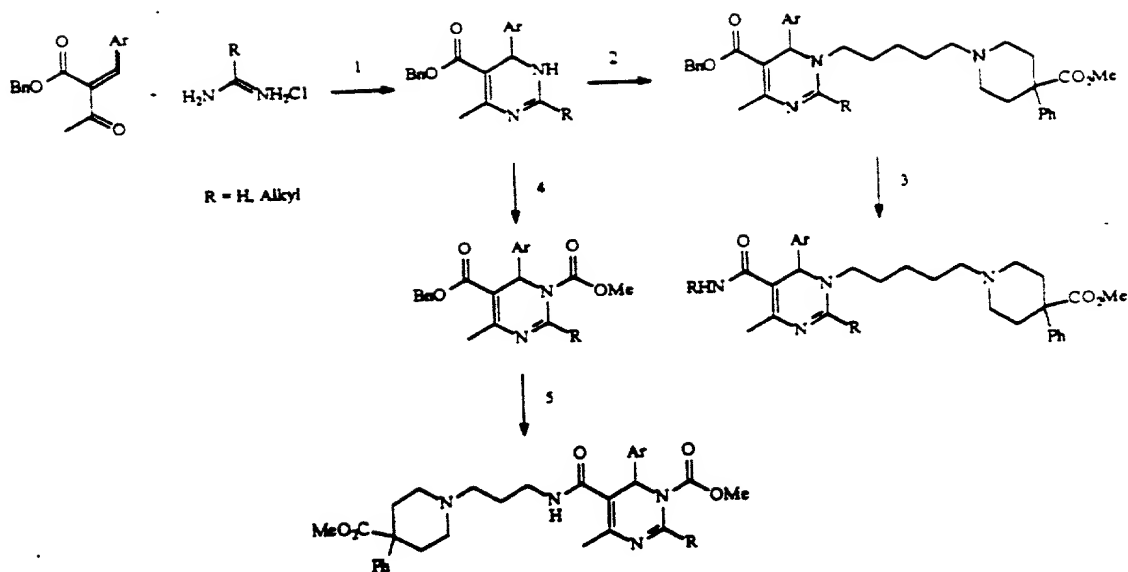




Scheme 19. Preparation of example 32

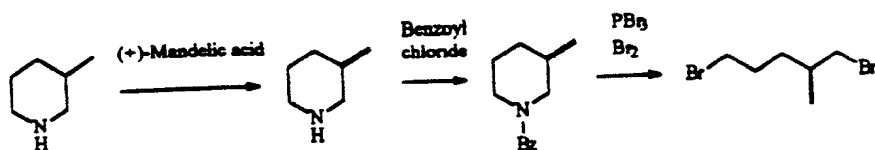


Scheme 20. Preparation of examples 38 and 46

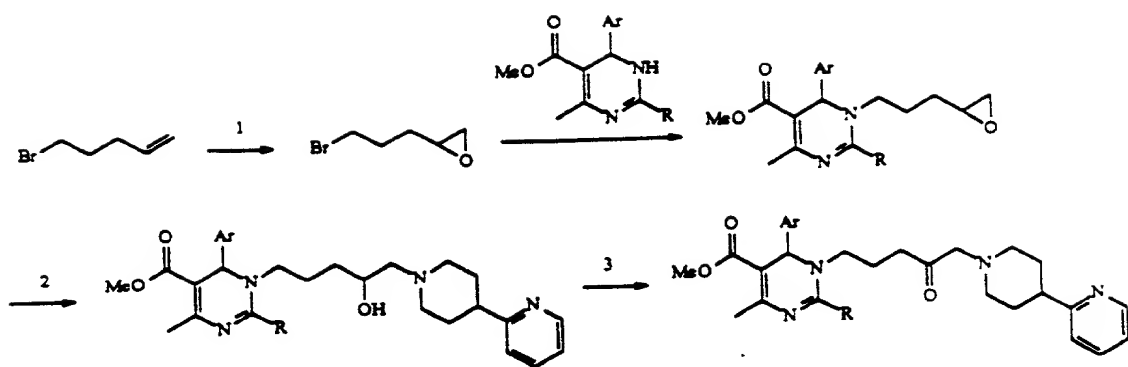


1. (a) KtBuO, DMF; (b) TsOH·H<sub>2</sub>O, DMF, 100-110°C.
2. (a) NaH, THF, 1,5-dibromopentane; (b) 4-Methoxycarbonyl-4-phenylpiperidine, K<sub>2</sub>CO<sub>3</sub>, dioxane.
3. (a) H<sub>2</sub>, Pd/C, MeOH. (b) CH<sub>3</sub>NH<sub>2</sub>, DMAPECD, CH<sub>2</sub>Cl<sub>2</sub>.
4. NaH, ClCO<sub>2</sub>Me, THF.
5. (a) H<sub>2</sub>, Pd/C, MeOH. (b) 3-(4-Methoxycarbonyl-4-phenylpiperidin-1-yl)propylamine, DMAPECD, CH<sub>2</sub>Cl<sub>2</sub>.

**Scheme 21 (part-2).** Synthetic scheme for examples 49, 50 and 51.

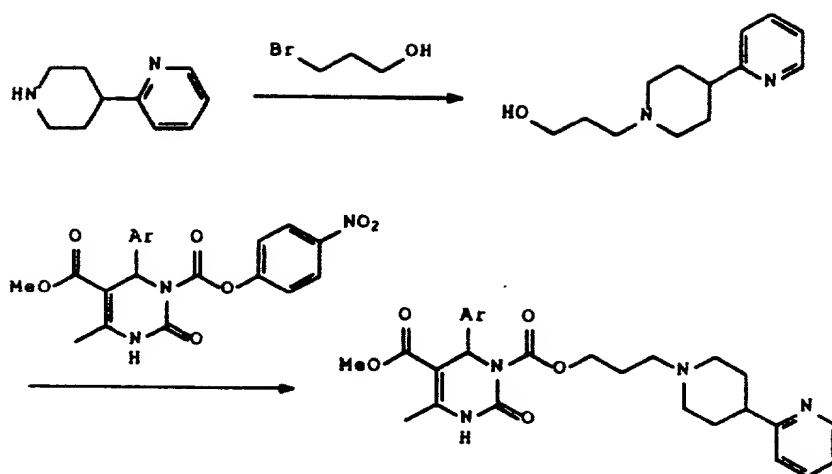


**Scheme 21 (part-1).** Synthesis of (S)-(-)-2-methyl-1,5-dibromopentane (Thurkauf et al. *J. Org. Chem.* 1987, 52, 5466-5467).

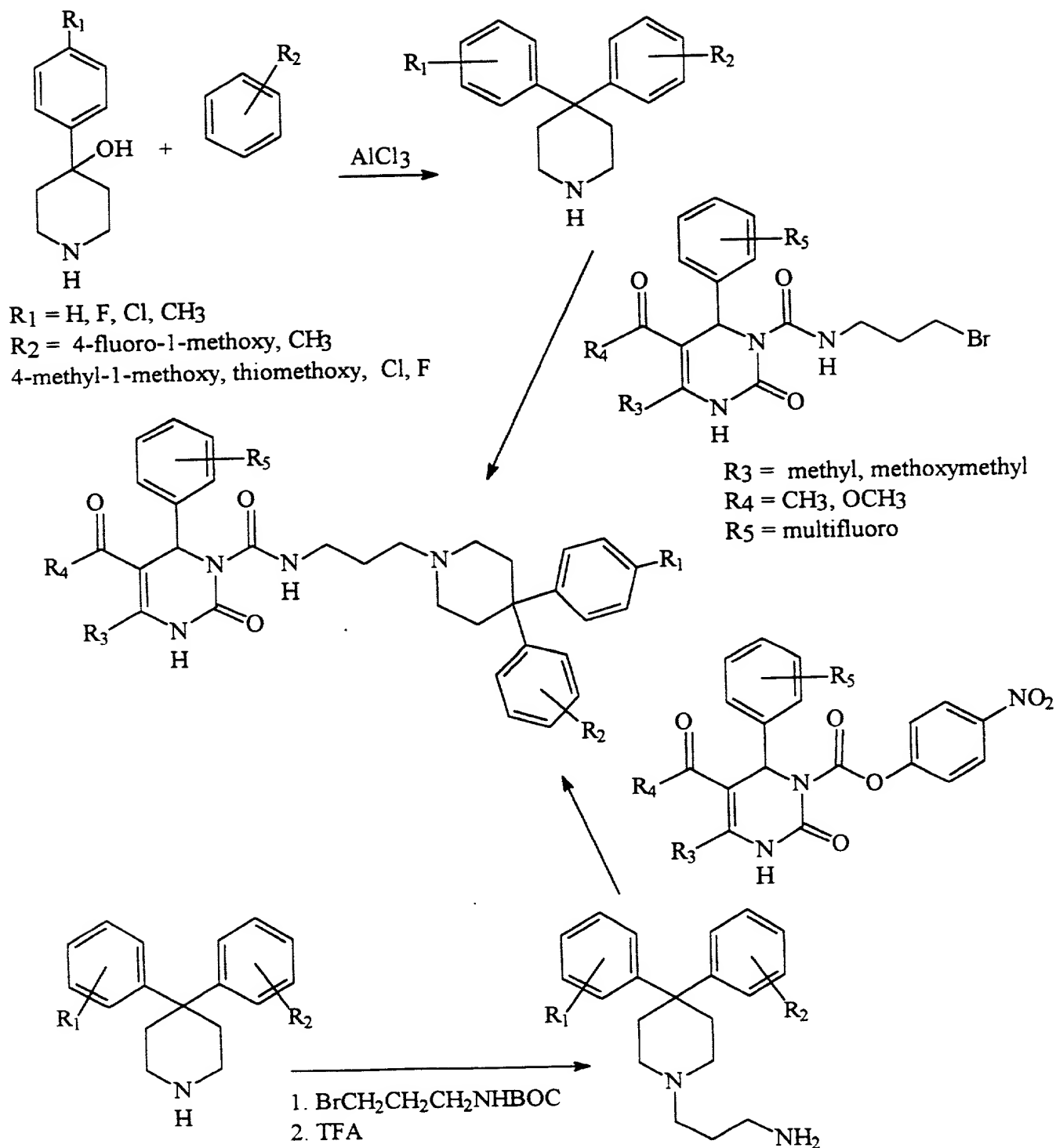


1. mCPBA,  $\text{CH}_2\text{Cl}_2$ .
2. 4-(2-Pyridyl)piperidine, dioxane.
3. Oxalyl chloride, DMSO,  $\text{CH}_2\text{Cl}_2$ .

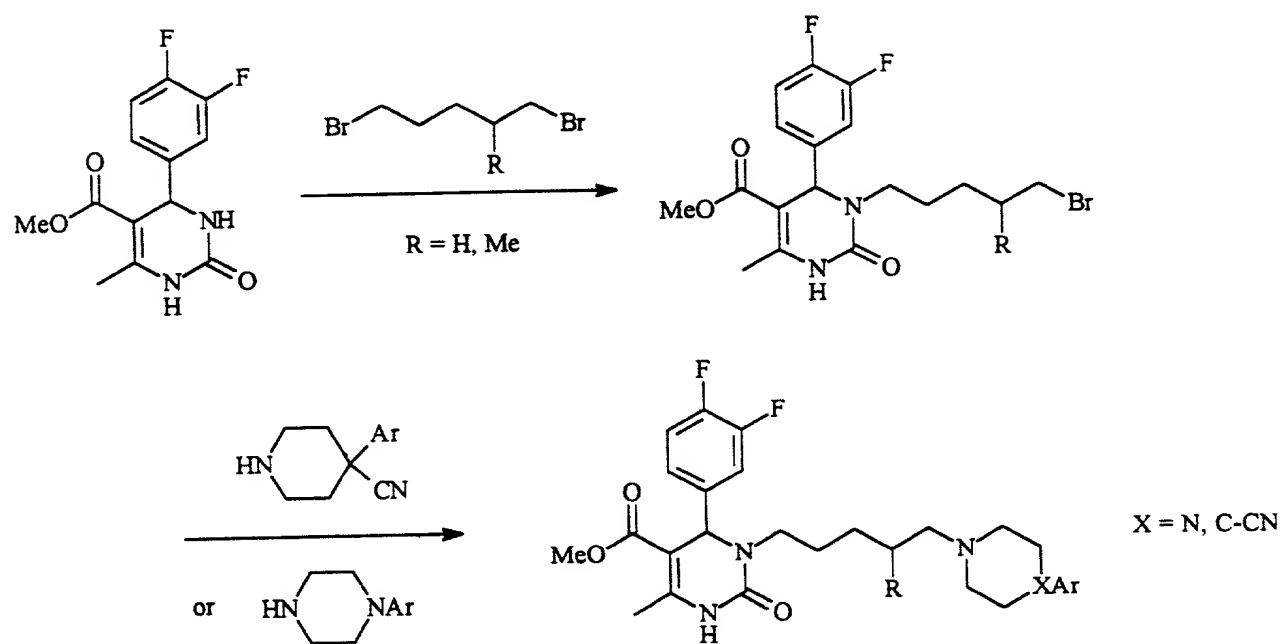
**Scheme 22.** Synthetic scheme for examples 56 and 57



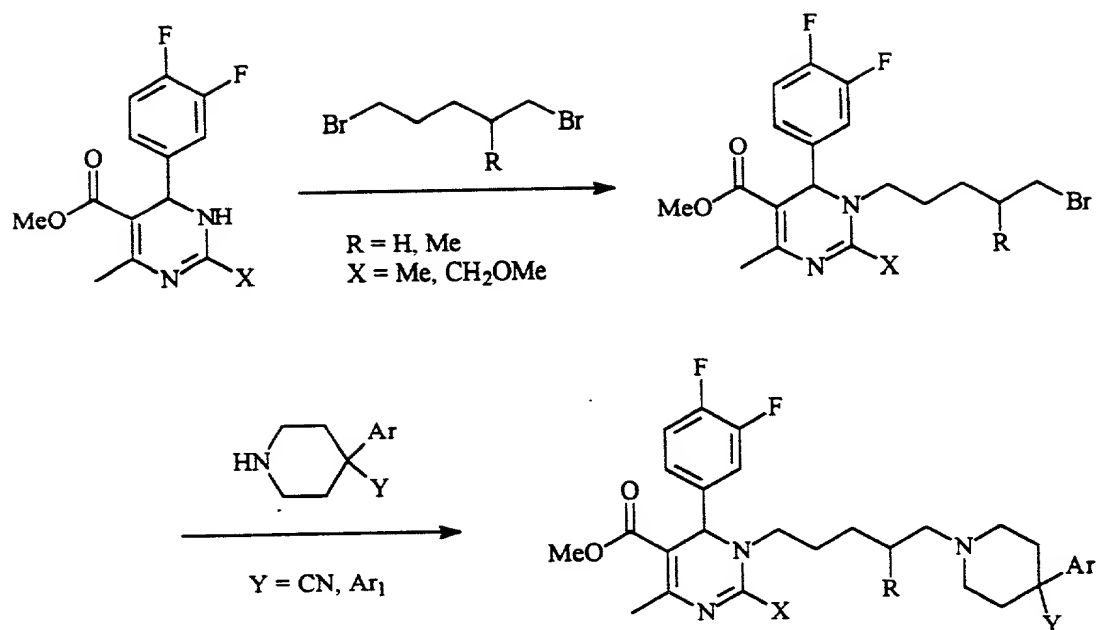
**Scheme 23.** Synthetic scheme for example 59



Scheme for the synthesis of examples 61-67.

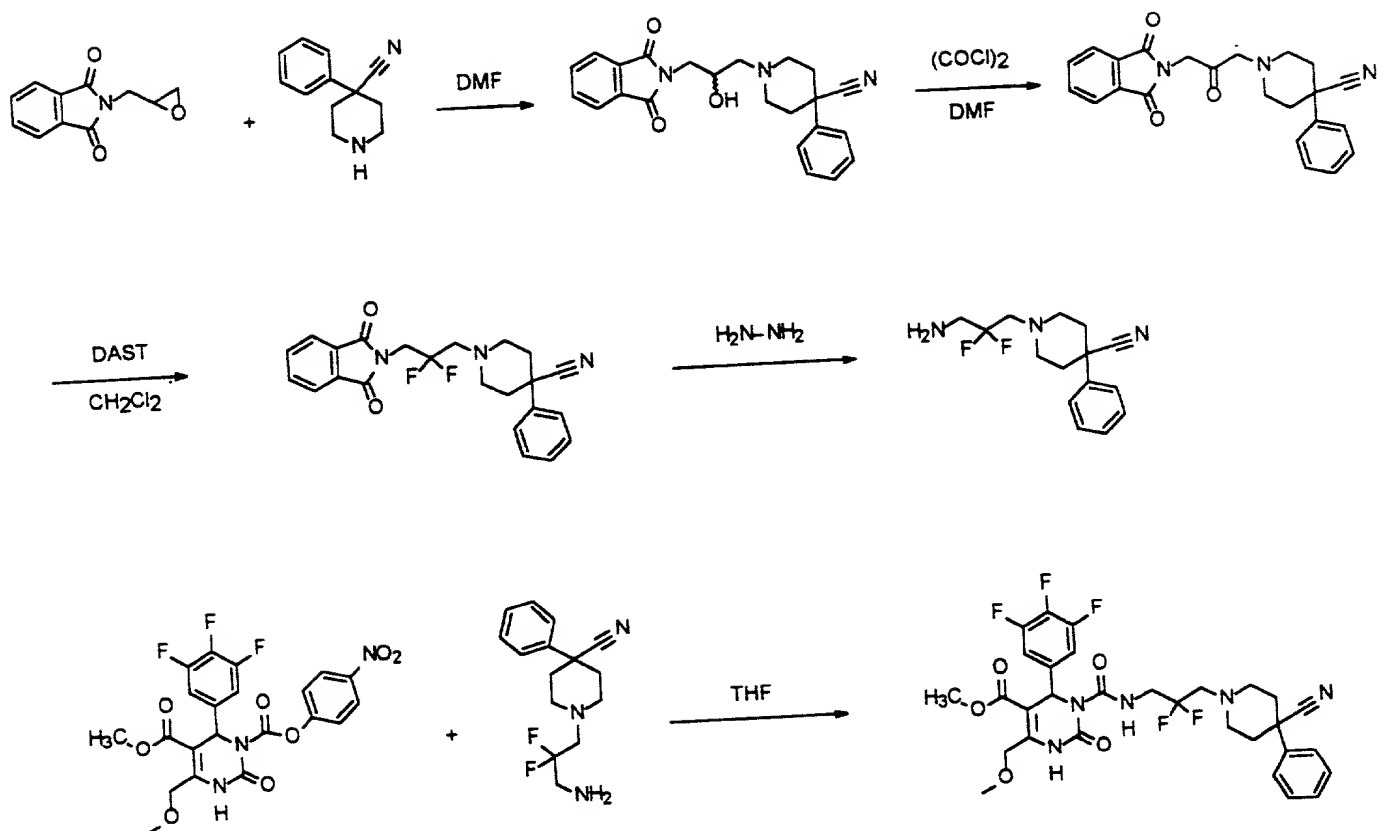


Synthetic scheme for examples 68 and 69.

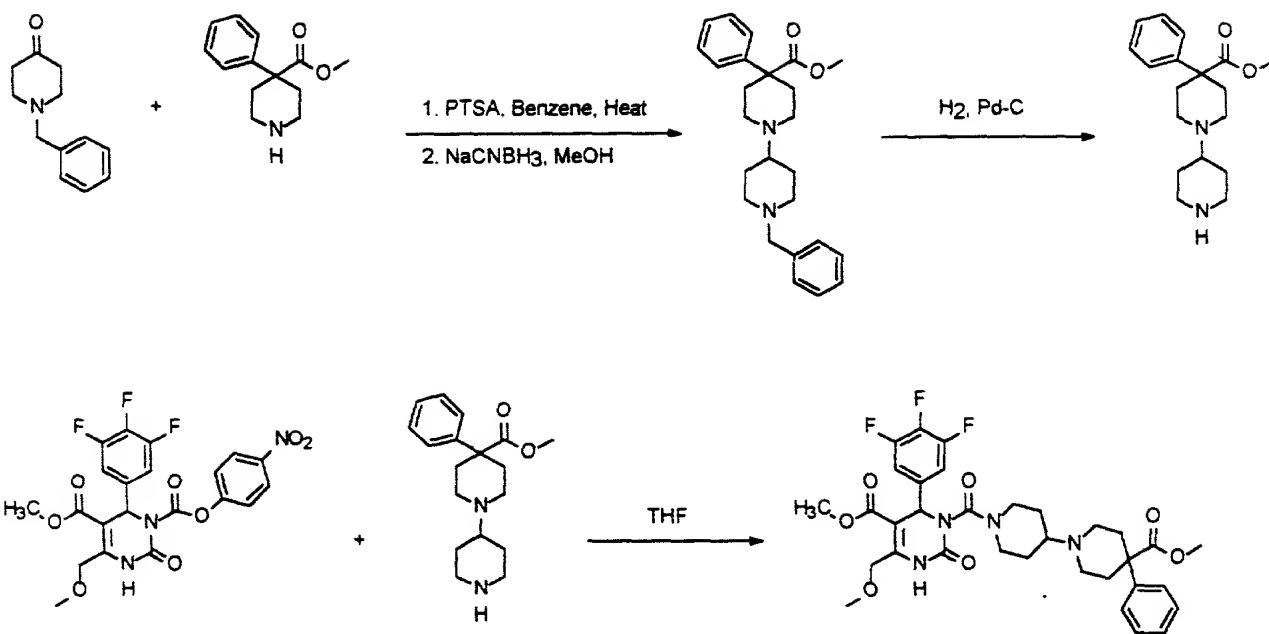


Synthetic scheme for examples 70-72.



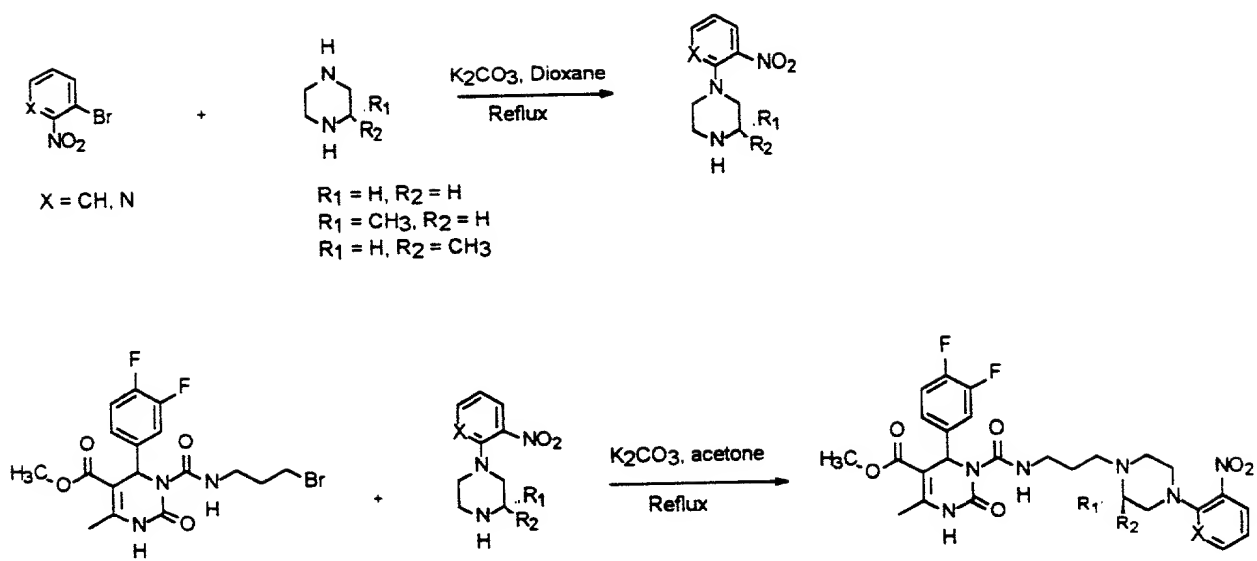


Scheme for the synthesis of example 76.

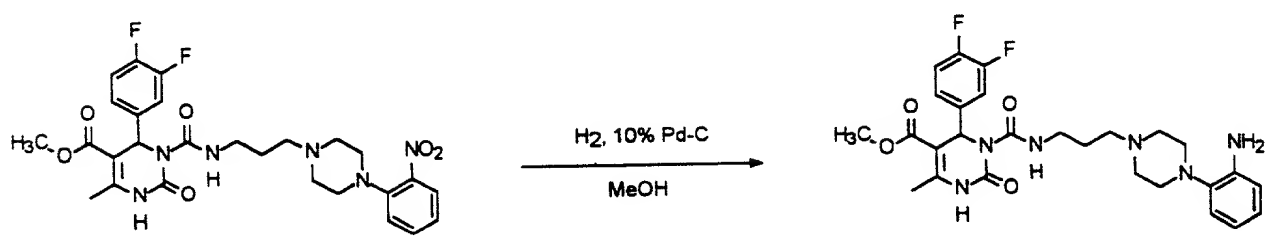


Scheme for the synthesis of example 77.

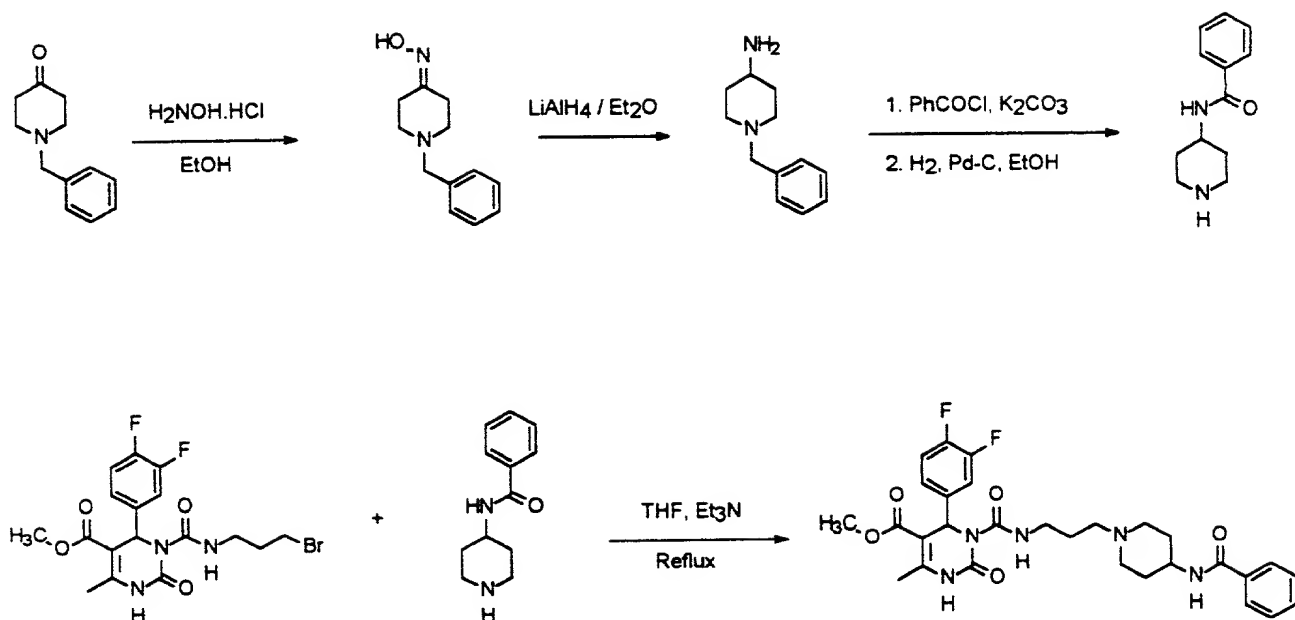




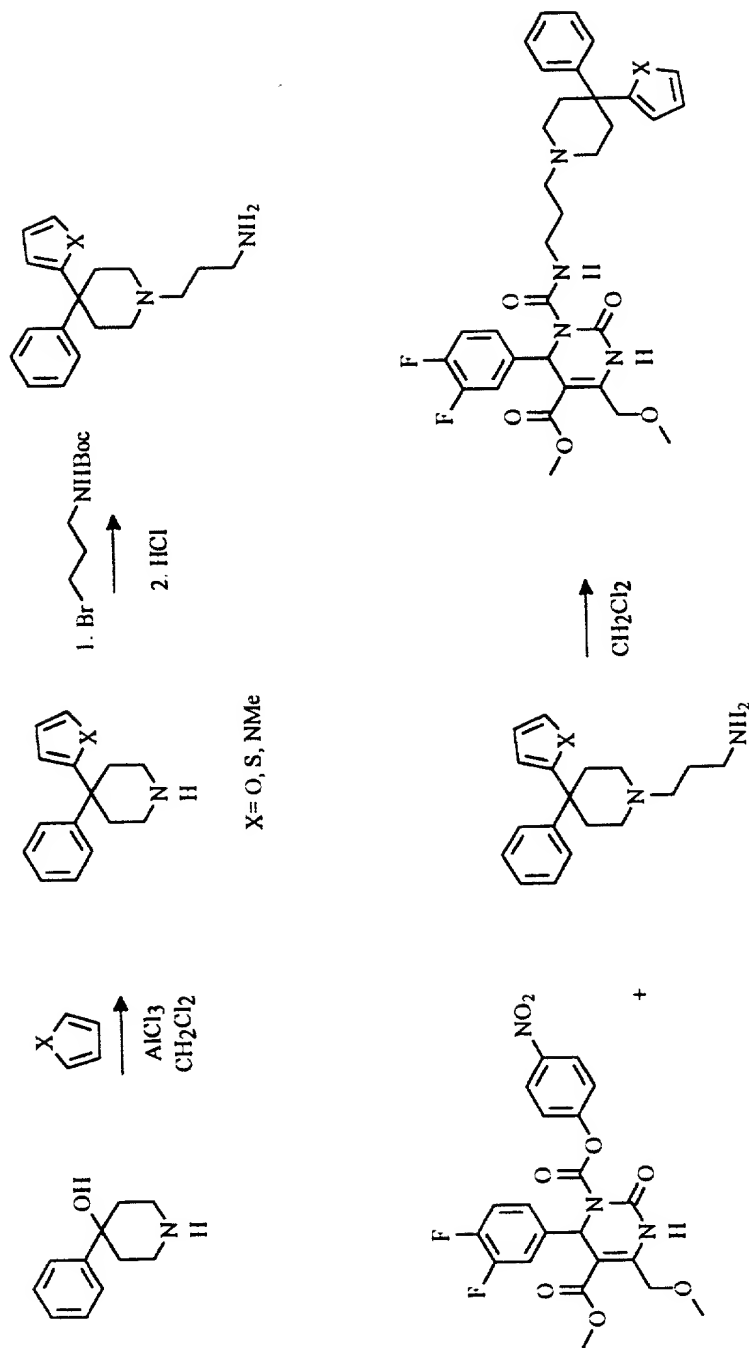
Scheme for the synthesis of examples 80, 82, 83 and 84.



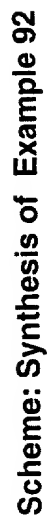
Scheme for the synthesis of example 81.

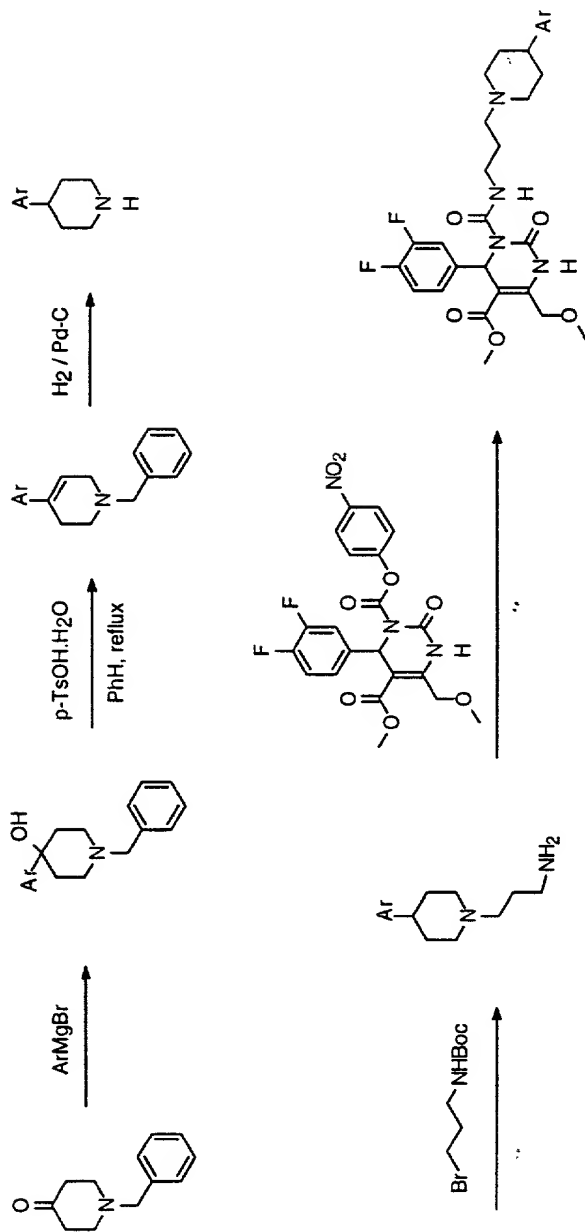


Scheme for the synthesis of example 88.



Synthetic scheme for examples 89-91.





**Scheme : Synthesis of examples 93, 94 and 95**